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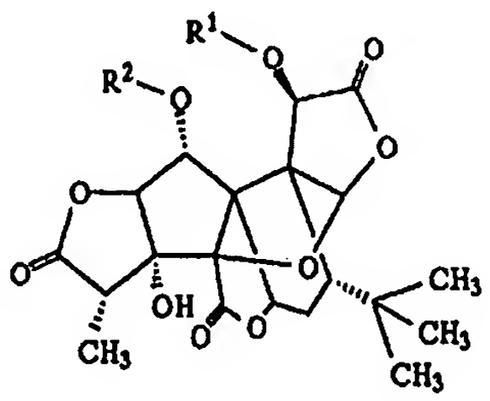

(I)

(57) Abstract

The present invention is directed to new ginkgolide derivatives, which may be used for the prevention or treatment of various PAF-induced diseases, and the pharmaceutical uses of theses derivatives. The present invention is also directed to a process for preparing these ginkgolide derivatives.

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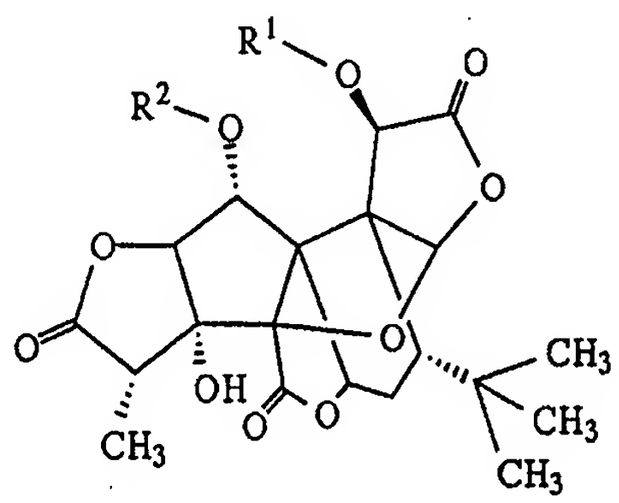
NEW GINKGOLIDE DERIVATIVES AND A PROCESS FOR PREPARING THEM

FIELD OF INVENTION

The present invention relates to new ginkgolide derivatives of formula (I), which have valuable PAF-antagonistic activity, and a process for preparing them, including a process for preparing Ginkgolide B derivatives and the pharmaceutical use of the derivatives. These compounds have excellent physiological activity.



(I)

BACKGROUND OF THE INVENTION

Benveniste et al. found a factor in 1972 which strongly induced platelet aggregation from rabbit basophils. This factor was named platelet-activating factor (hereinafter referred to simply as PAF). Hanahan et al. identified the factor in 1980 as a phosphoglyceride of the alkyl ether type having a acetyl group in the 2-position, i.e. 1-*O*-hexadecyl or octadecyl-2-acetyl-*sn*-glyceryl-3-phosphorylcholine.

The physiological roles of PAF have been intensively investigated, and it is known that PAF is an important factor in various physiological reactions, including platelet aggregation, reduction in blood pressure, immediate allergic reaction, contraction of smooth muscle, inflammation,

pain, edema, and alteration in the respiratory and circulatory systems.

Therefore, PAF-antagonistic activity-possessing compounds are very useful for treating various PAF-induced diseases, such as inflammatory diseases, allergic diseases, anaphylatic shocks, septic shocks, vascular diseases as DIC, myocardinal diseases, asthma, pulmonary edema, and adult respiratory diseases.

Compounds useful as therapeutic and prophylactic agents for cardiovascular diseases, such as, myocardial contractility impairment, thrombocytopenia, hypotension, anaphylaxis shock or endotoxin shock are disclosed in J. Pharmacol. Exp. Ther., 1985, 232, 156; Kidney Int., 1986, 29, 469; Pharmacol. Res. Commun., 1986, 18(suppl) 139, 173; Circulation, 1985, 72, 713; Prostaglandins, Leukotrienes and Liposins, Plenum press, New York, 1985, p.301; Eur. J. Pharmacol., 1984, 98, 357; Annu. Rev. Pharmacol. Toxicol., 1987, 27, 301; and Platelet-Activating Factor and Relates Lipid Mediations, Plenum Press, New York, 1987, p.403. Compounds useful as therapeutic and prophylactic agents for organ transplantation are disclosed in Transplantation, 1986, 42, 86; Eur. J. Clin. Invest., 1987, 17, 7; and Thromb. Haemostasis, 1987, 57, 125. Compounds useful as therapeutic and prophylactic agents for inflammatory, edema and immunophathological conditions are disclosed in Inflammation-Basic Principles and Clinical Correlates, Raven Press, New York, 1988, p. 13; Platelet-Activating Factor and Cell Immunology, Karger, Basel, 1988, vols 1 and 2; Drugs Future, 1988, 13, 137; and Immunol. Today, 1987, 8, 345. Compounds useful as therapeutic and prophylactic agents for asthma and respiratory conditions are disclosed in Trends Pharmacol. Sci., 1987, 8, 285; Drugs, 1988, 35, 93; Agents Actions, 1984, 15, 636; Eur. J. Respir. Dis., 1986, 68(suppl. 144), 163; Lancet, 1986, 2, 189; and Int. Arch.

Allergy Appl. Immunol., 1987, 82, 57. Compounds useful as therapeutic and prophylactic agents for pulmonary hypertension and adult respiratory distress syndrome(ARDS) are disclosed in Chest, 1983, 83 (suppl.), 785; Agents Actions, 1981, 11, 567; and Prostaglandins, 1983, 26, 457. Compounds useful as therapeutic and prophylactic agents for ischemia are disclosed in Platelet-Activating Factor and Structurally Related Alkyl Enter Lipids, American Oil Chemist's Society, p. 1236~1242, 1991; Biochem. Biophys. Res. Commun., 149, p.580~587, 1987; J. Neurochem., 151, p.88~109, 1988; Ann. N. Y. Acad. Sci., 559, p.1-16, 1989; and Pharmacol. Rev., 39, p.97~145, 1987. Compounds useful as therapeutic and prophylactic agents for ulcergenesis and gastrointestinal alterations are disclosed in Nature (London), 1986, 319, 54. Compounds useful as therapeutic and prophylactic agents for lethal anaphylatic shock are disclosed in Br. J. Pharmacol., 1984, 83, 125; Br. J. Pharmacol., 1983, 79, 595; Br. J. Pharmacol., 1987, 90, 203; and Prostaglandins, 1985, 30, 545.

Under these circumstances, investigations have been made on compounds having anti-PAF activity. Among these compounds, ginkgolide compounds (A, B , C, M and J), which are terpenoid compounds from the roots and leaves of the Ginkgo tree, have exhibited the PAF antagonistic activity described above. However, these compounds possess certain deficiencies in the areas of effects on the central nervous system, potency, effectiveness by oral administration, water solubility, effectiveness by intravenous administration and duration of activity. Therefore, there is a need for potent PAF-antagonistic ginkgolide compounds which possess not only effectiveness by oral administration, long lasting effect, water solubility and effedctiveness by intravenous administration, but also less inhibitory effects on the central nervous system.

Accordingly, the present inventors have conducted long term investigations and studies on ginkgolide derivatives which have not only excellent PAF-inhibiting activity, but also excellent physiological activity. The present invention has been accomplished based on these findings.

SUMMARY OF THE INVENTION

Accordingly, the present invention is directed to new ginkgolide derivatives, methods of preparing them and their pharmaceutical uses.

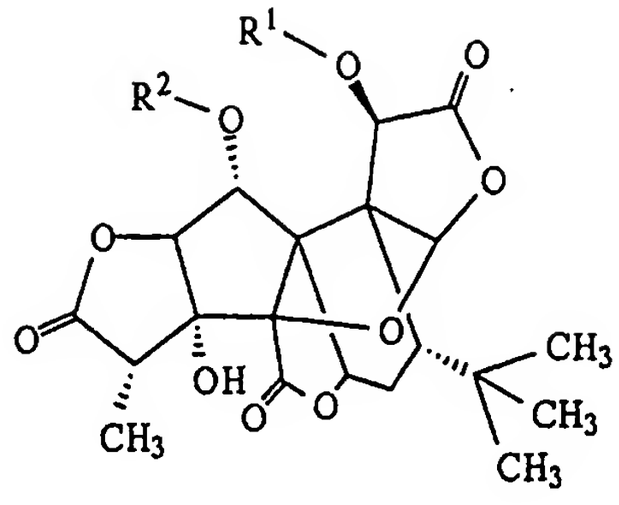
Additional features and advantages of the invention will be set forth in the description which follows, and in part will be apparent from the description or may be learned from practice of the invention. The advantages of the invention will be realized and attained by the compounds and processes particularly pointed out in the written description and claims.

To achieve these and other advantages and in accordance with the purpose of the invention, as embodied and broadly described, the invention provides new ginkgolide derivatives, which may be used for the prevention or treatment of various PAF-induced diseases, and the pharmaceutical uses of these derivatives. There is also provided a process for preparing these ginkgolide derivatives.

It is to be understood that both the foregiing general description and the following detailed description are exemplary and explanatory and are intended to provide further explanation of the invention as claimed.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to the new ginkgolide derivatives of the formula(I) :



(I)

wherein ,

R^2 represents hydrogen or R^1 group, and

R^1 represents -A-Ar, -A-Z-Ar, -C(=O)-Ar, $-SO_2$-Ar, -A-Het. or -A-NR^4R^5,

in which

A represents alkylene group having 1 to 8 carbon atoms, which is unsubstituted or substituted by a straight or branched alkyl chain having 1 to 5 carbon atoms,

Z represents carbon, oxygen, sulfur or nitrogen,

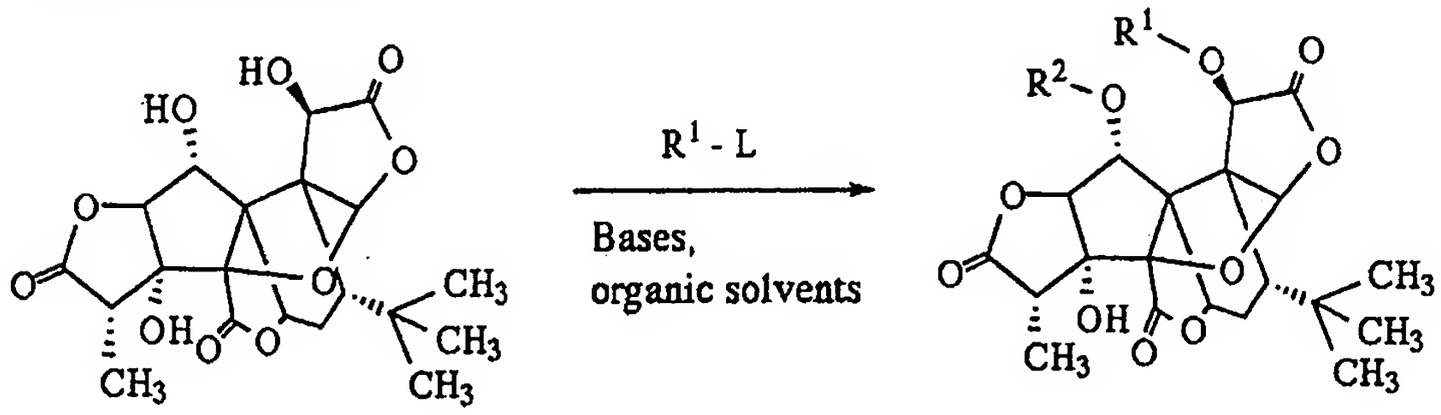
Ar represents a phenyl group, a pyridyl group, a naphthyl group, a pyrimidyl group, or a quinolyl group, each of which is unsubstituted or substituted by one to five substituents selected from the group consisting of hydrogen, halogen, a hydroxy group, a carboxylic acid group, an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 1 to 10 carbon atoms, an alkynyl group having 1 to 10 carbon atoms, a haloalkyl group having 1 to 10 carbon atoms, an alkoxy group having 1 to 10 carbon atoms, an alkenyloxy group having 1 to 10 carbon atoms, an alkynyloxy group having 1 to 10 carbon atoms, a haloalkoxy group having 1 to 10 carbon atoms, a phenyl group, a phenoxy group, an aralkyl group, an aralkyloxy group, a substituted phenyl group, a substituted phenoxy group, a substituted aralkyl group, a substituted aralkyloxy group, -COR^4, -$CONR^4R^5$, -CO_2R^4, -$NHCOR^4$, -NH(OH), -$N(OH)COR^4$, -CH_2OR^4,-$OCH_2CO_2R^4$, -CH_2SR^4,

$-CH_2NR^4R^5$, $-SR^4$, $-OSR^4$, $-SO_2NR^4R^5$, $-NR^4R^5$, $-NR^4SO_2R^5$ (in which R^4 and R^5 are the same or different and each is hydrogen, an alkyl group having 1 to 10 carbon atoms or a cycloalkyl group having 3 to 10 carbon atoms), $-SCX_3$(in which X represents halogen), -CN, $-NO_2$ and -Z-A-Z'-(in which Z and A are as defined above and Z' represents carbon, oxygen, sulfur, or nitrogen),

Het. represents a cyclic saturated or unsaturated heterocyclic group having one or more nitrogen, oxygen, and/or sulfur atoms, and

R^4 and R^5 represent the same or different and each is hydrogen, an alkyl group having 1 to 10 carbon atoms or a cycloalkyl group having 3 to 10 carbon atoms.

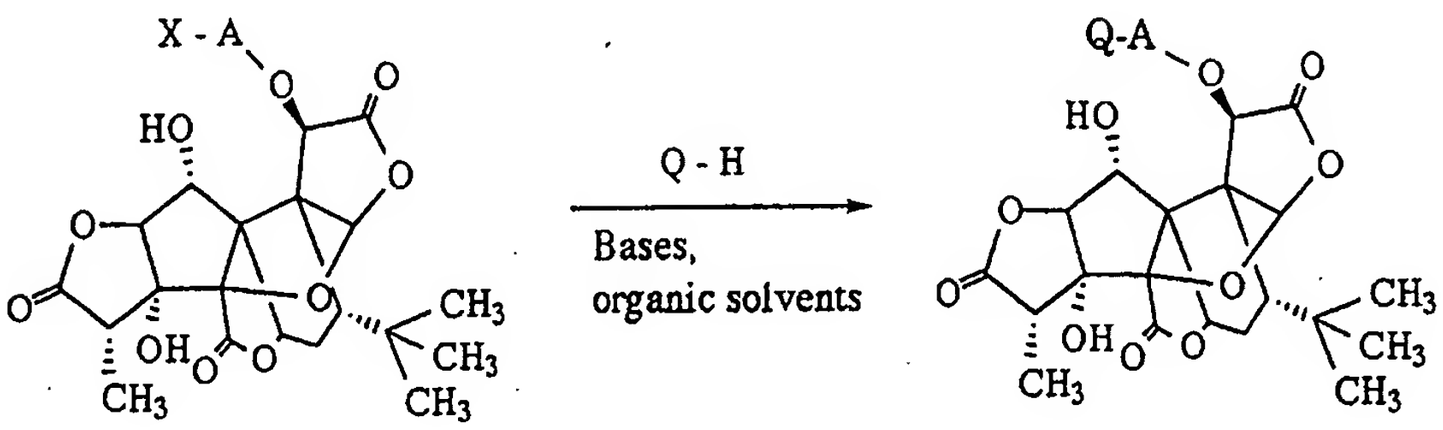
Also, the present invention relates to the process for preparing the new ginkgolide derivatives of the formula(I). The compounds of formula(I) can be prepared by reacting a compound of the formular R^1-L and the known Ginkgolide B of the formula(II) in the presence of bases and organic solvents.



(II) (I)

In the above reaction, R^1 and R^2 are as defined above, and L represents halogen atom(for example, fluorine, chlorine, bromine and iodine), 4-metylbenzenesulfonyloxy, methanesulfonyloxy, 4-nitrobenzenesulfonyloxy, 4-bromobenzenesulfonyloxy or trifluoromethanesulfonyloxy.

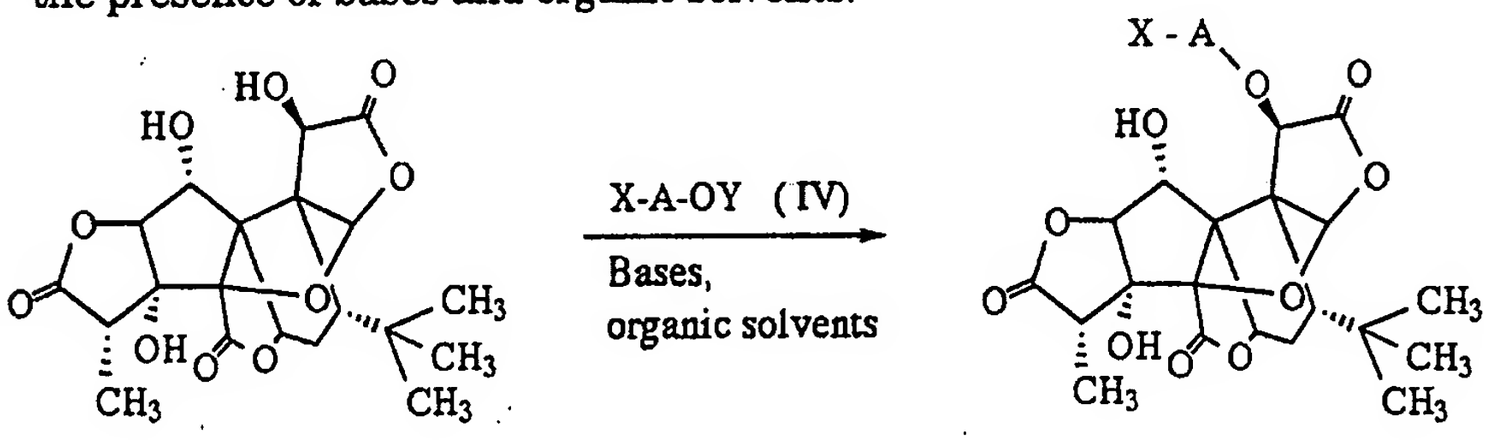
The present invention relates to the process for preparing the new ginkgolide derivatives of formula(I') by reacting a compound of the formula(III) with a compound of formula Q-H.



(III) (I')

In the above reaction, A is as defined above, Q is Het. or NR^4R^5 (in which Het., R^4 and R^5 are as defined above) , and X represents halogen atom(fluorine, chlorine, bromine and iodine).

The compounds of the above formula(III) can be prepared by reacting a compound of formula(IV) and the known Ginkgolide B of formula(II) in the presence of bases and organic solvents.



(II) (III)

In the above reaction, X and A are as defined above, Y represents 4-methylbenzenesulfonyl, methanesulfonyl, 4- nitrobenzenesulfonyl, 4-bromobenzenesulfonyl, or trifluoromethanesulfonyl .

The detailed description of preferred embodiments of the present invention compounds follows. Preferably, R^1 and R^2 in the above formula(I) are as shown below:

R^2 represents hydrogen or R^1 group, and

R^1 represents -A-Ar, -A-Z-Ar, -CO-Ar, -SO_2-Ar, -A-Het. or -A-NR^4R^5, in which A represents an alkylene group having 1 to 8 carbon atoms, for example, methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, heptamethylene or octamethylene group, which is unsubstituted or substituted by a straight or branched chain alkyl group having 1 to 5 carbon atoms, such as methylmethylene, propylene, methyltrimethylene, dimethylethylene, dimetyltetramethylene, ethylethylene or dimethyltrimethylene group ; Z represents carbon, oxygen, sulfur or nitrogen; Ar represents a phenyl group, a pyridyl group(including, for example, 1-pyridyl, 2-pyridyl, 3-pyridyl and 4-pyridyl group), a naphthyl group, a pyrimidyl group, or a quinolyl group, each of which is unsubstituted or substituted by one to five substituents; Het. represents saturated or unsaturated heterocyclic group having one or more nitrogen, oxygen, and/or sulfur atoms, for example, morpholinyl, piperidinyl, piperazinyl, triazolyl, imidazolyl, pyrrolidyl, thiazolidinyl or furanyl.

In the above definitions, the term "substituents" in Ar includes hydrogen; halogen including, for example, fluorine, chlorine, bromine or iodine ; hydroxy group; a carboxylic acid group ; an alkyl group having 1 to 10 carbon atoms, including, for example, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl, *n*-pentyl, isopentyl, 1-methylbutyl, *n*-hexyl, 1-methylpentyl, *n*-heptyl, 4-methylhexyl, 1-ethylpentyl, 1,4-dimetylpentyl, *n*-octyl, 6-methylheptyl or 2-ethylhexyl; an alkenyl group having 1 to 10 carbon atoms, including, for example, vinyl, allyl, 3-pentenyl or 1-hexenyl;

an alkynyl group having 1 to 10 carbon atoms, including, for example, acetynyl group ; a haloalkyl group having 1 to 10 carbon atoms, including, for example, fluoromethyl, chloromethyl, bromomethyl, iodomethyl, trifluoromethyl, trifluoroethyl, trifluoropropyl , trifluoromethylethyl or trifluoromethylpropyl; an alkoxy group having 1 to 10 carbon atoms, including, for example, methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, isobutoxy, *tert*-butoxy, *n*-pentyloxy, isopentyloxy, *n*-hexyloxy, *n*-heptyloxy, 1-propylbutoxy, *n*-octyloxy, 5-methylhexyloxy, 2-ethylhexyloxy or 1,6-dimethylhexyloxy; an alkenyloxy group having 1 to 10 carbon atoms; an alkynyloxy group having 1 to 10 carbon atoms ; a haloalkoxy group having 1 to 10 carbon atoms ; a phenyl group ; a phenoxy group ; an aralkyl group, including, for example, benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl or 4-phenylbutyl; an aralkyloxy group, including, for example, benzyloxy, 2-phenylethoxy, 3-penylpropoxy or 4-phenylbutoxy; a substituted phenyl group, including, for example, 2-chlorophenyl, 2-bromophenyl, 2-fluorophenyl, 2-iodophenyl, 3-fluorophenyl, 2,3-dichlorophenyl, 4-hydroxyphenyl, 2-methylphenyl, 4-methylphenyl, 3-ethylphenyl, 4-propylphenyl, 4-isopropylphenyl, 4-butylphenyl, 4-*tert*-butylphenyl, 4-pentylphenyl, 2,4-dimethylphenyl group, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 3-ethoxyphenyl, 2-propoxyphenyl, 4-butoxyphenyl or 2,4-dimethoxyphenyl ; a substituted phenoxy group, including, for example, 3,4,5-trimethoxyphenoxy, 2-chlorophenoxy, 2,3-dichlorophenoxy, 4-hydroxyphenoxy, 2-methoxyphenoxy, 4-butylphenoxy or 2,4-dimethylphenoxy; a substituted aralkyl group, including, for example, chlorobenzyl, bromobenzyl, fluorobenzyl, iodobenzyl, dichlorobenzyl, dibromobenzyl, difluorobenzyl, hydroxybenzyl, methylbenzyl, halomethylbenzyl, methoxybenzyl or trimethoxybenzyl; a

substituted aralkyloxy group, including, for example, chlorobenzyloxy, dimethylbenzyloxy, trifluoromethylbenzyloxy or trimethoxybenzyloxy; -COR^4 ; -$CONR^4R^5$; -CO_2R^4 ; $NHCOR^4$; N(OH)H ; $N(OH)COR^4$; -CH_2OR^4 ; -$OCH_2CO_2R^4$; -CH_2SR^4 ; -$CH_2NR^4R^5$; -SR^4 ; -OSR^4 ; -$SO_2NR^4R^5$; -NR^4R^5 ; -$NR^4SO_2R^4$ (in which R^4 and R^5 are the same or different and each is hydrogen, an alkyl group having 1 to 10 carbon atoms or a cycloalkyl group having 3 to 10 carbon atoms); -SCX_3(in which X represents halogen) ; -CN ; -NO_2 ; or cyclic linked substituent, -Z-A-Z'- (in which Z and A are as defined above and Z' represents carbon, oxygen, sulfur, or nitrogen) including, for example, -OCH_2O-,-OCH_2CH_2O-, -$OCH_2CH_2CH_2O$-, -OCH_2CH_2N-, -NCH_2CH_2N-, -OCH_2CH_2-, -NCH_2CH_2-, -$NCH_2CH_2CH_2$-, -SCH_2S-, -SCH_2CH_2S-, -SCH_2-, -SCH_2CH_2- or -$SCH_2CH_2CH_2$-.

Particularly preferred compounds of the present invention are the compounds of formula(I) wherein R^2 is hydrogen, and R^1 is -CH_2-Ar, -CH_2CH_2-Ar, -$CH_2CH_2CH_2$-Ar, -CH_2O-Ar, -CH_2CH_2O-Ar, -$CH_2CH_2CH_2O$-Ar, $-\overset{O}{\overset{\|}{C}}$-Ar or -$SO_2$-Ar,

in which Ar is a phenyl group, a pyridyl group, a pyrimidyl group, a quinolyl group, each of which is unsubstituted or substituted by one to five substituents selected from the group consisting of hydrogen, halogen, a hydroxy group, an alkyl group having 1 to 10 carbon atoms, an haloalkyl group having 1 to 10 carbon atoms, an alkoxy group having 1 to 10 carbon atoms, a haloalkoxy group having 1 to 10 carbon atoms, a phenyl group, a phenoxy group, an aralkyl group, an aralkyloxy group, $-\overset{O}{\overset{\|}{C}}R^4$, $-\overset{O}{\overset{\|}{C}}NR^4R^5$, -$CO_2R^4$, -$CH_2OR^4$, -$NR^4R^5$, -$CH_2NR^4R^5$, -CN, -$NO_2$ and -Z-A-Z'-, wherein R^4, R^5, Z, A and Z' are as defined above.

More particularly preferred compounds of the present invention are the compounds selected from the group consisting of

10-benzyloxy-Ginkgolide B,

10-(2',4'-dichlorobenzyloxy)-Ginkgolide B,

10-(4'-chlorobenzyloxy)-Ginkgolide B,

10-(4'-methoxybenzyloxy)-Ginkgolide B,

10-(3',4',5',-trimethoxybenzyloxy)-Ginkgolide B,

10-(2'-methylbenzyloxy)-Ginkgolide B,

1, 10-bis(2'-methylbenzyloxy)-Ginkgolide B,

10-(4'-methylbenzyloxy)-Ginkgolide B,

10-(3'-phenoxypropoxy)-Ginkgolide B,

10-(2'-phenylethoxy)-Ginkgolide B,

10-(3',4',5',-trimethoxybenzoyloxy)-Ginkgolide B,

10-(4'-phenylbenzyloxy)-Ginkgolide B,

10-piperonyloxy-Ginkgolide B,

10-(2',3',4',5',6'-pentafluorobenzyloxy)-Ginkgolide B,

10-(2',4'-difluorobenzyloxy)-Ginkgolide B,

10-(4'-fluorobenzyloxy)-Ginkgolide B,

10-(2'-fluorobenzyloxy)-Ginkgolide B,

10-benzoyloxy-Ginkgolide B,

1-benzoyloxy-Ginkgolide B,

1,10-bis(2',4'-dichlorobenzyloxy)-Ginkgolide B,

10-(3'-trifluoromethylbenzyloxy)-Ginkgolide B,

10-benzenesulfonyloxy-Ginkgolide B,

10-(3'-methoxybenzyloxy)-Ginkgolide B,

10-(4'-trifluoromethylbenzyloxy)-Ginkgolide B,

1,10-bis(4'-trifluoromethylbenzyloxy)-Ginkgolide B,

10-(4'-hydroxybenzyloxy)-Ginkgolide B,

10-(4'-ethoxybenzyloxy)-Ginkgolide B,

10-(3'-bromobenzyloxy)-Ginkgolide B,

10-(4'-iodobenzyloxy)-Ginkgolide B,

10-(2',3',4'-trihydroxybenzyloxy)-Ginkgolide B,

10-(2'-iodobenzyloxy)-Ginkgolide B,

10-(2'-hydroxybenzyloxy)-Ginkgolide B,

10-(3'-iodobenzyloxy)-Ginkgolide B,

10-(3'-hydroxybenzyloxy)-Ginkgolide B,

10-(2'-bromobenzyloxy)-Ginkgolide B,

10-(3',4'-dihydroxybenzyloxy)-Ginkgolide B,

10-(4'-bromobenzyloxy)-Ginkgolide B,

10-(2'-chlorobenzyloxy)-Ginkgolide B,

10-(3'-chlorobenzyloxy)-Ginkgolide B,

10-(2',4',-dibromobenzyloxy)-Ginkgolide B,

10-(2',3',4',5',6'-pentachlorobenzyloxy)-Ginkgolide B,

10-(2',3',4',5',6'-pentabromobenzyloxy)-Ginkgolide B,

10-(2',3',4',5',6'-pentaiodobenzyloxy)-Ginkgolide B,

10-(2'-methoxybenzyloxy)-Ginkgolide B,

10-(3'-methoxybenzyloxy)-Ginkgolide B,

10-(2'-ethoxybenzyloxy)-Ginkgolide B,

10-(3'-ethoxybenzyloxy)-Ginkgolide B,

10-(2'-propoxybenzyloxy)-Ginkgolide B,

10-(3'-propoxybenzyloxy)-Ginkgolide B,

10-(4'-propoxybenzyloxy)-Ginkgolide B,

10-(2'-isopropoxybenzyloxy)-Ginkgolide B,

10-(3'-isopropoxybenzyloxy)-Ginkgolide B,

10-(4'-isopropoxybenzyloxy)-Ginkgolide B,

10-(4'-methlbenzyloxy)-Ginkgolide B,

10-(2'-ethylbenzyloxy)-Ginkgolide B,

10-(3'-ethylbenzyloxy)-Ginkgolide B,

10-(4'-ethylbenzyloxy)-Ginkgolide B,

10-(2'-propylbenzyloxy)-Ginkgolide B,

10-(3'-propylbenzyloxy)-Ginkgolide B,

10-(2'-bromoethoxy)-Ginkgolide B,

10-(2'-iodoethoxy)-Ginkgolide B,

10-(2'-(1"-piperidinyl)-ethoxy)-Ginkgolide B,

10-(2'-(1"-morphorinyl)-ethoxy)-Ginkgolide B,

10-(2'-(1"-(1",2",4"-triazolyl)-ethoxy))-Ginkgolide B,

10-(2'-(1"-piperazinyl))-Ginkgolide B,

10-(2'-(1"-pyrrolidinyl)-ethoxy)-Ginkgolide B,

10-(3,5-dimethyl-2-pyridinyl)-methoxy-Ginkgolide B,

10-(4-methoxy-3,5-dimethyl-2-pyridinyl)-methoxy-Ginkgolide B,

10-(3,5-dimethyl-4-nitro-2-pyridinyl)-methoxy-Ginkgolide B,

10-(2-pyridinyl)-methoxy-Ginkgolide B,

10-(5-butyl-2-pyridinyl)-methoxy-Ginkgolide B,

10-(2-pyridinyl)-ethoxy-Ginkgolide B,

10-(2-quinolinyl)-methoxy-Ginkgolide B,

10-(3,5-dimethyl-4-amino-2-pyridinyl)-methoxy-Ginkgolide B,

10-(3,5-dimethyl-4-nitro-2-pyridnyl)-methoxy-Ginkgolide B,

10-(3,5-dimethyl-4-hydroxy-2-pyridinyl)-methoxy-Ginkgolide B,

10-(3,5-dimethyl-4-hydroxyamino-2-pyridinyl)-methoxy-Ginkgolide B,

10-(4-benzoylamino-3,5-dimethyl-2-pyridinyl)-methoxy-Ginkgolide B,

10-(4-*N*-benzoyl-*N*-hydroxyamino-3,5-dimethyl-2-pyridinyl-methoxy-

Ginkgolide B,

10-(6-chloro-3-pyridinyl)-methoxy-Ginkgolide B,

10-(3-pyridinyl)-methoxy-Ginkgolide B,

10-(4-pyridinyl)-methoxy-Ginkgolide B,

10-(2-(4-ethoxypyridinyl))-methoxy-Ginkgolide B,

10-(2-(4-nitropyridinyl))-methoxy-Ginkgolide B,

10-(2-(6-methyl-3-propoxypyridinyl))-methoxy-Ginkgolide B,

10-(2-(4-hydroxyaminopyridinyl))-methoxy-Ginkgolide B,

10-(2-(5-methoxyethoxymethoxypyridinyl))-methoxy-Ginkgolide B,

10-(2-(5-hydroxypyridinyl))-methoxy-Ginkgolide B,

10-(4'-propylbenzyloxy)-Ginkgolide B,

10-(2'-isopropylbenzyloxy)-Ginkgolide B,

10-(3'-isopropylbenzyloxy)-Ginkgolide B,

10-(4'-isopropylbenzyloxy)-Ginkgolide B,

10-(2'-butylbenzyloxy)-Ginkgolide B,

10-(3'-butylbenzyloxy)-Ginkgolide B,

10-(4'-butylbenzyloxy)-Ginkgolide B,

10-(4'-pentylbenzyloxy)-Ginkgolide B,

10-(2',3'-dihydroxybenzyloxy)-Ginkgolide B,

10-(2',4'-dihydroxybenzyloxy)-Ginkgolide B,

10-(2',5'-dihydroxybenzyloxy)-Ginkgolide B,

10-(2',6'-dihydroxybenzyloxy)-Ginkgolide B,

10-(3',5'-dihydroxybenzyloxy)-Ginkgolide B,

10-(3',6'-dihydroxybenzyloxy)-Ginkgolide B,

10-(3',4',5'-trihydroxybenzyloxy)-Ginkgolide B,

10-(2'-vinylbenzyloxy)-Ginkgolide B,

10-(3'-vinylbenzyloxy)-Ginkgolide B,

10-(4'-vinylbenzyloxy)-Ginkgolide B,

10-(2'-allylbenzyloxy)-Ginkgolide B,

10-(2'-trifluoromethylbenzyloxy)-Ginkgolide B,

10-(2'-trichloromethylbenzyloxy)-Ginkgolide B,

10-(3'-trichloromethylbenzyloxy)-Ginkgolide B,

10-(4'-trichloromethylbenzyloxy)-Ginkgolide B,

10-(2'-tribromomethylbenzyloxy)-Ginkgolide B,

10-(3'-tribromomethylbenzyloxy)-Ginkgolide B,

10-(4'-tribromomethylbenzyloxy)-Ginkgolide B,

10-(2'-fluoromethylbenzyloxy)-Ginkgolide B,

10-(3'-allylbenzyloxy)-Ginkgolide B,

10-(4'-allylbenzyloxy)-Ginkgolide B,

10-(3'-fluoromethylbenzyloxy)-Ginkgolide B,

10-(4'-fluoromethylbenzyloxy)-Ginkgolide B,

10-(2'-chloromethylbenzyloxy)-Ginkgolide B,

10-(3'-chloromethylbenzyloxy)-Ginkgolide B,

10-(4'-chloromethylbenzyloxy)-Ginkgolide B,

10-(2'-bromomethylbenzyloxy)-Ginkgolide B,

10-(3'-bromomethylbenzyloxy)-Ginkgolide B,

10-(4'-bromomethylbenzyloxy)-Ginkgolide B,

10-(2'-fluoromethoxybenzyloxy)-Ginkgolide B,

10-(3'-fluoromethoxybenzyloxy)-Ginkgolide B,

10-(4'-fluoromethoxybenzyloxy)-Ginkgolide B,

10-(2'-chloromethoxybenzyloxy)-Ginkgolide B,

10-(3'-chloromethoxybenzyloxy)-Ginkgolide B,

10-(4'-chloromethoxybenzyloxy)-Ginkgolide B,

10-(2'-bromomethoxybenzyloxy)-Ginkgolide B,

10-(3'-bromomethoxybenzyloxy)-Ginkgolide B,

10-(4'-bromomethoxybenzyloxy)-Ginkgolide B,

10-(2'-trifluoromethoxybenzyloxy)-Ginkgolide B,

10-(3'-trifluoromethoxybenzyloxy)-Ginkgolide B,

10-(4'-trifluoromethoxybenzyloxy)-Ginkgolide B,

10-(2'-trichloromethoxybenzyloxy)-Ginkgolide B,

10-(3'-trichloromethoxybenzyloxy)-Ginkgolide B,

10-(4'-trichloromethoxybenzyloxy)-Ginkgolide B,

10-(2'-tribromomethoxybenzyloxy)-Ginkgolide B,

10-(3'-tribromomethoxybenzyloxy)-Ginkgolide B,

10-(4'-tribromomethoxybenzyloxy)-Ginkgolide B,

10-(2'-phenoxybenzyloxy)-Ginkgolide B,

10-(2'-benzylbenzyloxy)-Ginkgolide B,

10-(3'-phenoxybenzyloxy)-Ginkgolide B,

10-(3'-benzylbenzyloxy)-Ginkgolide B,

10-(4'-phenoxybenzyloxy)-Ginkgolide B,

10-(4'-benzylbenzyloxy)-Ginkgolide B,

10-(1'-phenethoxy)-Ginkgolide B,

10-(3'-phenpropoxy)-Ginkgolide B,

10-(4'-phenbutoxy)-Ginkgolide B,

10-(4'-(2"-phenethyl)-benzyloxy)-Ginkgolide B,

10-(4'-(1"-phenethyl)-benzyloxy)-Ginkgolide B,

10-(4'-(3"-phenpropyl)-benzyloxy)-Ginkgolide B,

10-(4'-(4"-phenbutyl)-benzyloxy)-Ginkgolide B,

10-(4'-(2"-chlorophenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(2"-bromophenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(2"-fluorophenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(2"-bromophenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(2"-iodophenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(3"-fluorophenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(2",3"-dichlorophenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(4"-hydroxyphenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(2"-methylphenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(4"-methylphenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(3"-ethylphenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(4"-propylphenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(4"-isopropylphenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(4"-butylphenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(4"-pentylphenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(2",4"-dimethylphenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(2"-trifluoromethylphenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(2"-methoxyphenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(3"-methoxyphenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(4"-methoxyphenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(3"-ethoxyphenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(2"-propoxyphenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(4"-butoxyphenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(2",4"-dimethoxyphenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(3",4",5"-trimethoxyphenoxy)-benzyloxy)-Ginkgolide B,

10-(4'-(2"-chlorophenoxy)-benzyloxy)-Ginkgolide B,

10-(4'-(2",3"-dichlorophenoxy)-benzyloxy)-Ginkgolide B,

10-(4'-(4"-hydroxyphenoxy)-benzyloxy)-Ginkgolide B,

10-(4'-(2"-methoxyphenoxy)-benzyloxy)-Ginkgolide B,

10-(4'-(4"-butylphenoxy)-benzyloxy)-Ginkgolide B,

10-(4'-(2",4"-dimethylphenoxy)-benzyloxy)-Ginkgolide B,

10-(4'-(4"-chlorobenzyl)-benzyloxy)-Ginkgolide B,

10-(4'-(4"-bromobenzyl)-benzyloxy)-Ginkgolide B,

10-(4'-(4"-fluorobenzyl)-benzyloxy)-Ginkgolide B,

10-(2'-nitrobenzyloxy)-Ginkgolide B,

10-(3'-nitrobenzyloxy)-Ginkgolide B,

10-(4'-nitrobenzyloxy)-Ginkgolide B,

10-(2'-cyanobenzyloxy)-Ginkgolide B,

10-(3'-cyanobenzyloxy)-Ginkgolide B,

10-(4'-cyanobenzyloxy)-Ginkgolide B,

10-(2'-aminobenzyloxy)-Ginkgolide B,

10-(3'-aminobenzyloxy)-Ginkgolide B,

10-(4'-aminobenzyloxy)-Ginkgolide B,

10-(2'-dimethylaminobenzyloxy)-Ginkgolide B,

10-(3'-dimethylaminobenzyloxy)-Ginkgolide B,

10-(4'-dimethylaminobenzyloxy)-Ginkgolide B,

10-(3',4'-dihydroxybenzyloxy)-Ginkgolide B,

10-(3,5-dimethyl-4-hydroxybenzyloxy)-Ginkgolide B,

10-(3,5-di-*tert*-butyl-4-hydroxybenzyloxy)-Ginkgolide B,

10-(4-hydroxy-3-methoxybenzyloxy)-Ginkgolide B,

10-(3,5-dimethoxy-4-hydroxybenzyloxy)-Ginkgolide B and

10-(3-amino-4-hydroxy-5-methyl-benzyloxy)-Ginkgolide B.

The present invention further provides the pharmacological use of the compound of formula(I) defined above. According to the present invention, a pharmaceutical composition is provided which comprises a pharmacologically effective amount of a compound of formula(I) and a pharmacologically acceptable carrier.

The present invention also provides a method for treating a disease against which anti-PAF activity is effective, which comprises administering a pharmacologically effective amount of a compound of formula(I) to a host in need. The disease which may be treated in this manner include allergic disease such as asthma, inflammatory disease, septic shock and anaphylactic shock, vascular disease such as DIC, myocardial disease, pulmonary edema and adult respiratory disease.

To prepare compounds of the formula(I), the compounds of the formula(II) defined above may be reacted with a compound of formula R^1-L defined above.

This reaction is usually carried out for 1 to 10 hours at 0~70 ℃ in a solvent(e.g., tetrahydrofuran, acetone, ethyl acetate, dimethyl formamide, dimethyl sulfoxide, pyridine, dioxane, methanol, ethanol, 2-methoxyethanol or a mixed solvent thereof) in the presence of an easily available base.

These easily available bases include, for example, Ag_2O, triethylamine, an alkalicarbonate, an alkalibicarbonate, an alkali hydroxide, MH, wherein M is alkali metal such as Li, Na and K etc.(e.g., lithium hydride, sodium hydride or potassium hydride), MNH_2(e.g., sodium amide, etc.), MOR^4, MR^4, R^4R^5NM, $MN(TMS)_2$ and mixtures thereof (R^4 and R^5 are the same as defined above and TMS is trimethylsilyl group).

Also, for preparing compounds of formula(I'), compounds of formula(III) defined above may be reacted with a compund of formula Q-H as defined above either in the presence of solvent and base or in the absence of solvent and base.

In the above reaction, the reaction is usually carried out for 1 to 10 hours at 0~90 ℃ in a solvent(e.g., tetrahydrofuran, acetone, ethyl acetate, dimethyl formamide, dimethyl sulfoxide, pyridine, dioxane, methanol, 2-

methoxyethanol or a mixtures thereof) in the presence of an easily available base as defined above.

The compounds of the formula(I') may also be prepared from the compounds of the formula(III) and Q-H directly, i.e. in the absence of solvent and base. In this reaction, it is especially preferable to conduct the reaction at 0~90℃ due to the slowness of the reaction below 0 ℃ and the presence of side reactions above 90 ℃, which result in low yields.

Also, compounds of formula(III) may be prepared by reacting a compound of the formula(II) and a compound of the formula(IV) in a mixed organic solvent as defined above in the presence of an easily available base for 1 to 10 hours at 0~90 ℃. In this reaction, the organic solvent and base are the same as employed in the preparation of compound of the formula(I) defined above.

In accordance with the present invention, from study of the structure-activity relationship of Ginkgolide derivatives having substituents at the C-1 and/or C-10 position, the new Ginkgolide B derivative is useful as a PAF-antagonistic agent.

The following examples more fully illustrate the present invention, but the invention is not intended to be limited thereby.

Example 1. 10-benzyloxy-Ginkgolide B

To a solution of 50 ㎎ of Ginkgolide B in 5 *㎖* of tetrahydrofuran was added 16 ㎎ of potassium hydride followed by stirring, in an inert atmosphere, at room temperature for 5 minutes. To the mixture was, then added 60 ㎎ of benzylbromide, followed by stirring at room temperature for 4 hours.

The mixture was treated with 0.5 *㎖* of c-HCl at 0 ℃, diluted with 10 *㎖* of water and extracted with 50 *㎖* of ethylacetate. The solution was

washed with 10 *ml* of water and dried over anhydrous magnesium sulfate.

After filtering off, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on silica gel(elution solvent: chloroform / methanol=99 /1) to give 51 mg(85 %) of the desired compound.

^{1}H-NMR ($CDCl_3$) ; δ 7.38~7.31(m, 5H), 6.44(s, 1H), 6.16(s, 1H), 5.32(brs, 1H), 5.25(s, 1H), 5.02(ABq, 2H, J=11.4Hz, $\Delta\upsilon$ =193Hz), 4.71(d, 1H, J=4.5Hz), 4.60(d, 1H, J=6.9Hz), 4.17(dd, 1H, J=6.9, 4.5Hz), 2.87(q, 1H, J=6.9Hz), 2.14(dd, 1H, J=13.5Hz, 3.6Hz), 1.86(td, 1H), 1.75(dd, 1H), 1.12(d, 1H, J=6.9Hz), 1.02(s, 9H)

Example 2. 10-(2',4'-dichlorobenzyloxy)-Ginkgolide B

To a solution of 50 mg of Ginkgolide B in 5 *ml* of tetrahydrofuran was added 16 mg of potassium hydride followed by stirring, in an inert atmosphere, at room temperature for 5minutes.

To the mixture was, then added 118 mg of 2,4-dichlorobenzyl iodide, followed by stirring at room temperature for 4 hours.

The mixture was treated with 0.5 *ml* of c-HCl at 0 ℃, diluted with 10 *ml* of water and extracted with 50 *ml* of ethylacetate. The solution waswashed with 10 *ml* of water and dried over anhydrous magnesium sulfate.

After filtering off, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (elution solvent: chloroform / methanol = 99 / 1) to give 43 mg(62 %) of the desired compound.

^{1}H-NMR ($CDCl_3$) ; δ 7.47~7.33(m, 3H), 5.99(s, 1H), 5.35(brs, 1H), 5.19(ABq,

2H, J=9.9, $\Delta\upsilon$ =183Hz), 4.90(s, 1H), 4.54(d, 1H, J=7.8Hz), 4.24(dd, 1H, J=7.8, 2.4Hz), 3.04(q, 1H, J=6.9Hz), 2.91(s, 1H), 2.75(d, 1H, J=2.4Hz), 2.28(m, 1H), 1.95~1.92(m, 2H), 1.30(d, 3H, J=6.9Hz), 1.11(s, 9H)

Example 3. 10-(4'-chlorobenzyloxy)-Ginkgolide B

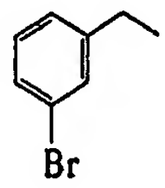
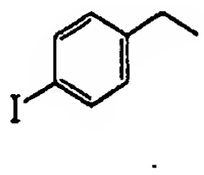
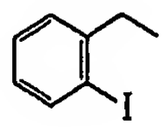
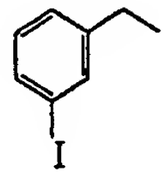
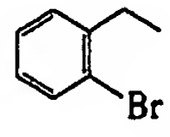
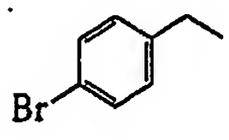
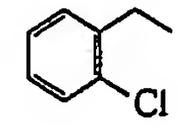
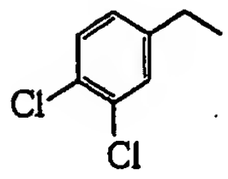
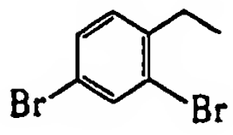
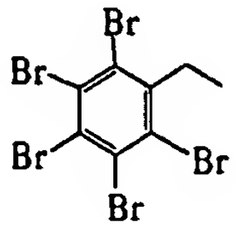
To a solution of 50 ㎎ of Ginkgolide B in 5 ㎖ of tetrahydrofuran was added 16 ㎎ of potassium hydride followed by stirring, in an inert atmosphere, at room temperature for 5 minutes. To the mixture was then added 104 ㎎ of 4-chlorobenzyliodide, followed by stirring at room temperature for 4 hours.

The mixture was treated with o.5 ㎖ of c-HCl at 0 ℃, diluted with 10 ㎖ of water and extracted with 50 ㎖ of ethylacetate. The solution was washed with 10 ㎖ of water and dried over anhydrous magnesium sulfate. After filtering off, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (elution solvent: chloroform / methanol = 99 / 1) to give 47 ㎎(72 %) of the desired compound.

^{1}H-NMR ($CDCl_3$) ; δ 7.42~7.39(m, 2H), 7.32~7.29(m, 2H), 5.99(s, 1H), 5.32(brs, 1H), 5.03(ABq, 2H, J=9.6, $\Delta\upsilon$ =270Hz), 4.90(s, 1H), 4.54(d, 1H, J=7.8Hz), 4.27(brs, 1H), 3.04(q, 1H, J=6.6Hz), 2.94(brs, 1H), 2.75(brs, 1H), 2.28(1H), 1.90(m, 2H), 1.28(d, 3H), 1.14(s, 9H).

Examples 4 to 13.

In the same manner as in the Example 3, the following compounds were prepared.

Example	R^1	R^2	m. p.(℃)
4		H	145 ~ 147
5		H	
6		H	
7		H	
8		H	
9		H	
10		H	
11		H	
12		H	152.1 ~ 153.2
13		H	

Example 14. 10-(4'-methoxybenzyloxy)-Ginkgolide B

To a solution of 50 ㎎ of Ginkgolide B in 5 *㎖* of tetrahydrofuran wasadded 16 ㎎ of potassium hydride followed by stirring, in an inert atmosphere, at room temperature for 5 minutes. To the mixture was then added 102 ㎎ of 4-methoxybenzyl iodide, followed by stirring at room temperature for 4 hours.

The mixture was treated with o.5 *㎖* of c-HCl at 0 ℃, diluted with 10 *㎖* of water and extracted with 50 *㎖* of ethylacetate. The solution was washed with 10 *㎖* of water and dried over anhydrous magnesium sulfate. After filtering off, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (elution solvent: chloroform / methanol = 99 / 1) to give 53 ㎎(82 %) of the desired compound.

^{1}H-NMR ($CDCl_3$) ; δ 7.30~7.26(m, 2H), 6.98~6.88(m, 2H), 5.98(s, 1H), 5.30(brs, 1H), 4.95(ABq, 2H, J=9.6Hz, $\Delta\upsilon$ =264Hz), 4.52(d, 1H, J=7.8Hz), 4.26(dd, 1H, J=7.8, 3.3Hz), 3.80(d, 3H, J=1.5Hz), 3.05(q, 1H, J=7.2Hz), 2.86(d, 1H, J=3.3Hz), 2.26(m, 1H), 1.92~1.89(m, 2H), 1.29(d, 3H), 1.14(s, 9H)

Example 15. 10-(3',4',5'-trimethoxybenzyloxy)-Ginkgolide B

To a solution of 50 ㎎ of Ginkgolide B in 5 *㎖* of tetrahydrofuran was added 16 ㎎ of potassium hydride followed by stirring, in an inert atmosphere, at room temperature for 5 minutes. To the mixture was then added 127 ㎎ of 3,4,5-trimethoxybenzyl iodide, followed by stirring at room temperature for 4 hours.

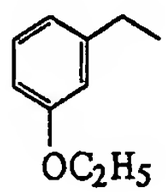
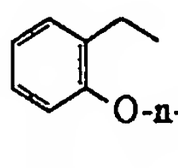
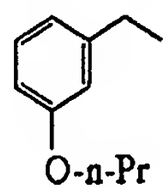
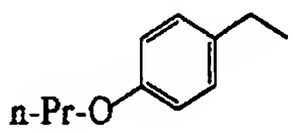
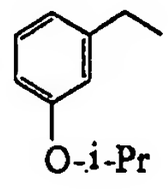
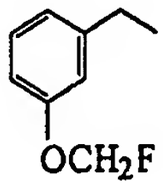
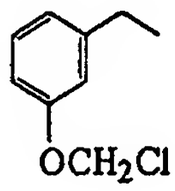
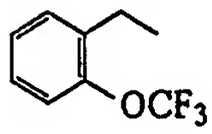
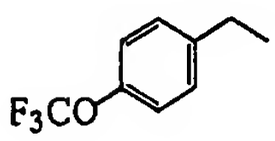
The mixture was treated with o.5 *㎖* of c-HCl at 0 ℃, diluted with 10

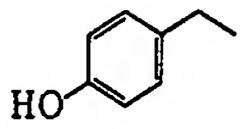
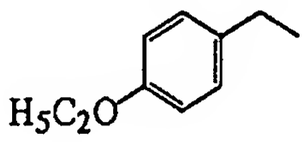
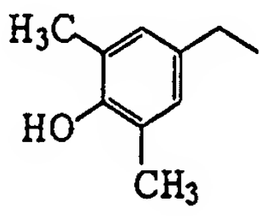
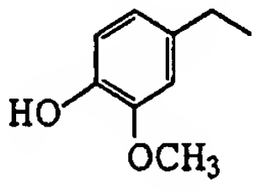
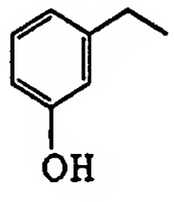
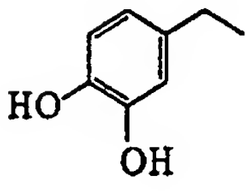
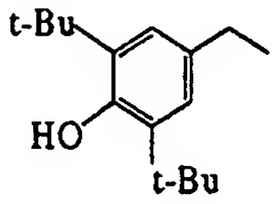
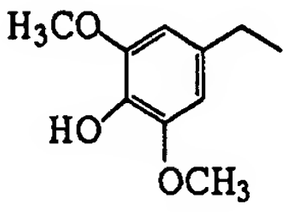
ml of water and extracted with 50 *ml* of ethylacetate. The solution was washed with 10 *ml* of water and dried over anhydrous magnesium sulfate. After filtering off, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (elution solvent: chloroform / methanol = 99 / 1) to give 48 mg(68 %) of the desired compound.

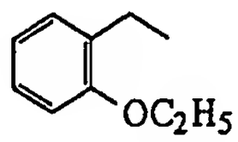
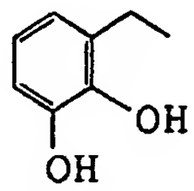
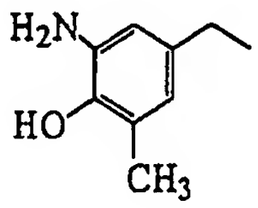
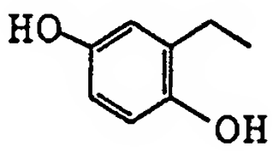
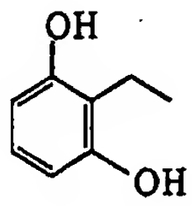
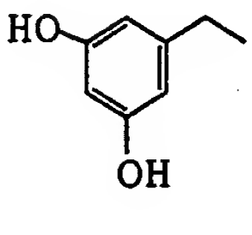
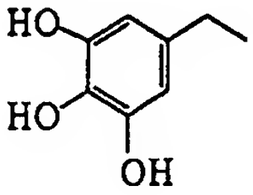
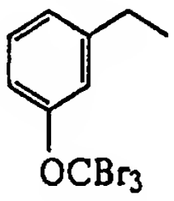
^{1}H-NMR ($CDCl_3$) ; δ 6.55(s, 2H), 6.00(s, 1H), 5.34(brs, 1H), 4.99(ABq, 2H, J=9.3Hz, $\Delta\upsilon$ =277Hz), 4.89(s, 1H), 4.56(d, 1H, J=7.8Hz), 3.95(dd, 1H, J=7.8, 3.0Hz), 3.87(d, 9H), 3.06(q, 1H, J=7.2Hz), 2.85(m, 1H), 2.0~1.80(m, 2H), 1.31(d, 3H, J=7.2Hz), 1.14(s, 9H).

Examples 16 to 40.

In the same manner as in the Example 15, the following compounds were prepared.

Example	R^1	R^2	m. p.(℃)
16		H	157.2 ~ 158.4
17		H	
18		H	
19		H	
20		H	
21		H	
22		H	
23		H	
24		H	142.1 ~ 144.5

Example	R^1	R^2	m. p.(℃)
25		H	201.2 ~ 203.4
26		H	
27		H	
28		H	
29		H	
30		H	
31		H	
32		H	

Example	R^1	R^2	m. p.(℃)
33		H	156.2 ~ 157.8
34		H	220.1 ~ 221.7
35		H	
36		H	
37		H	
38		H	
39		H	
40		H	148.2 ~ 149.7

Example 41. 10-(2'-methylbenzyloxy)-Ginkgolide B

To a solution of 50 ㎎ of Ginkgolide B in 5 *㎖* of tetrahydrofuran wasadded 16 ㎎ of potassium hydride followed by stirring, in an inert atmosphere, at room temperature for 5 minutes. To the mixture was then added 76 ㎎ of 2-methylbenzyl bromide, followed by stirring at room temperature for 4 hours.

The mixture was treated with o.5 *㎖* of c-HCl at 0 ℃, diluted with 10 *㎖* of water and extracted with 50 *㎖* of ethylacetate. The solution was washed with 10 *㎖* of water and dried over anhydrous magnesium sulfate. After filtering off, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (elution solvent: chloroform / methanol = 99 / 1) to give 57 ㎎(91 %) of the desired compound.

^{1}H-NMR ($CDCl_3$); δ 7.33~7.19(m, 4H), 5.99(s, 1H), 5.31(brs, 1H), 5.13(ABq, J=9.3Hz, $\Delta\upsilon$ =282Hz), 4.91(s,1H), 4.52(d,1H, J=8.1Hz), 4.23(dd, 1H, J=8.1, 3.0Hz), 3.05(q, 1H, J=6.9Hz), 2.90(s, H), 2.75(d, 1H, J=3.0Hz), 2.41(s, 3H), 2.27(m, 1H),1.98~1.90(m, 2H), 1.29(d, 3H, J=6.9Hz), 1.14(s, 9H).

Example 42. 1,10-bis(2'-methylbenzyloxy)-Ginkgolide B

To a solution of 50 ㎎ of Ginkgolide B in 5 *㎖* of tetrahydrofuran was added 16 ㎎ of potassium hydride followed by stirring, in an inert atmosphere, at room temperature for 5 minutes. To the mixture was then added 152 ㎎ of 2-methylbenzyl bromide, followed by stirring at room temperature for 4 hours.

The mixture was treated with 0.5 *㎖* of c-HCl at 0 ℃, diluted with 10 *㎖* of water and extracted with 50 *㎖* of ethylacetate. The solution was

washed with 10 *ml* of water and dried over anhydrous magnesium sulfate. After filtering off, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (elution solvent: chloroform / methanol = 99 / 1) to give 34 mg(45 %) of the desired compound.

^{1}H-NMR ($CDCl_3$) ; δ 7.22~6.84(m, 8H), 5.99(s, 1H), 5.69(d, 1H, J=3.6Hz), 5.02(ABq, 2H, J=11.1Hz, $\Delta\upsilon$ =177Hz), 4.83(s,1H), 3.99(d,1H, J=12.0Hz), 3.22(q, 1H, J=6.9Hz), 2.95(s, 1H),2.36~1.90(m,3H), 2.20(s, 3H), 1.98(s, 3H), 1.31(d, 3H, J=6.9Hz), 1.04(s, 9H).

Example 43. 10-(4'-methylbenzyloxy)-Ginkgolide B

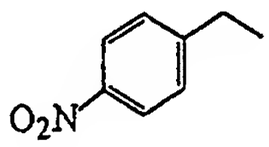
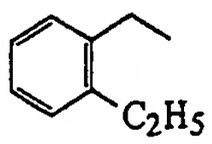
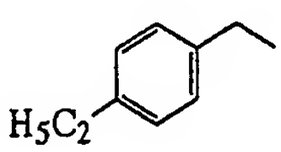
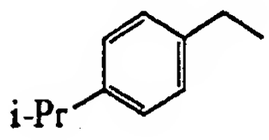
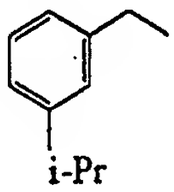
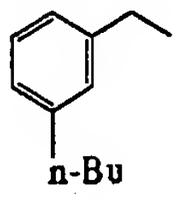
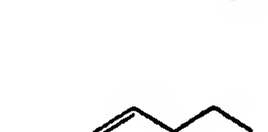
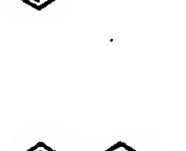
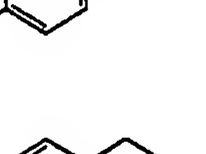
To a solution of 50 mg of Ginkgolide B in 5 *ml* of tetrahydrofuran was added 16 mg of potassium hydride followed by stirring, in an inert atmosphere, at room temperature for 5 minutes. To the mixture was then added 76 mg of 4-methylbenzyl bromide, followed by stirring at room temperature for 4 hours.

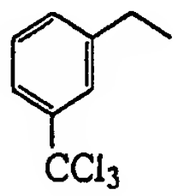
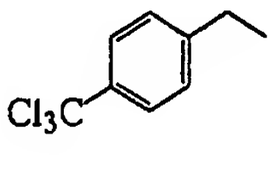
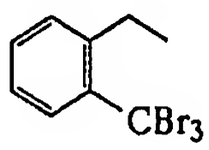
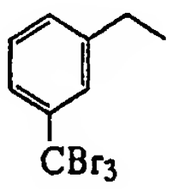
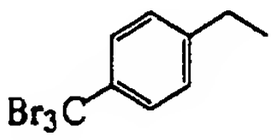
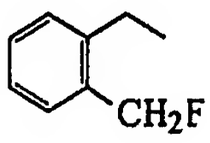
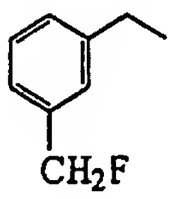
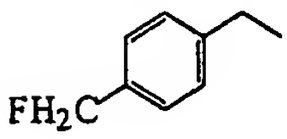
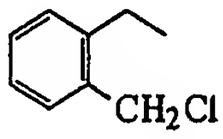
The mixture was treated with 0.5 *ml* of c-HCl at 0 ℃, diluted with 10 *ml* of water and extracted with 50 *ml* of ethylacetate. The solution was washed with 10 *ml* of water and dried over anhydrous magnesium sulfate. After filtering off, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (elution solvent: chloroform / methanol = 99 / 1) to give 55 mg(87 %) of the desired compound.

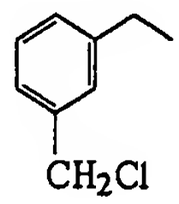
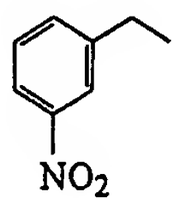
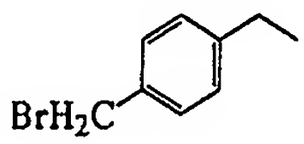
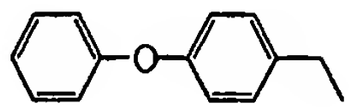
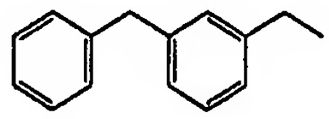
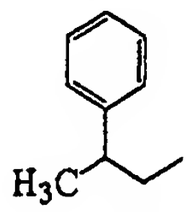
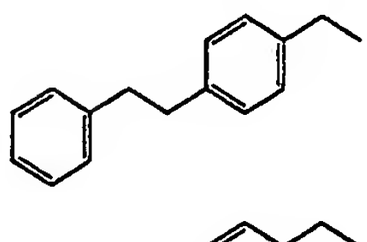
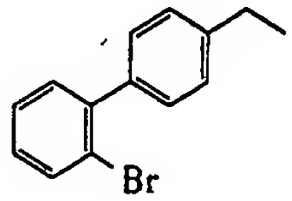
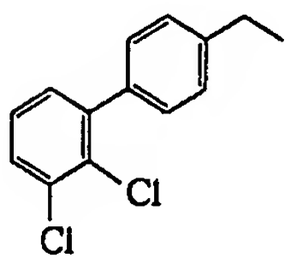
^{1}H-NMR ($CDCl_3$) ; δ 7.24~7.14(m, 4H), 5.98(s, 1H), 5.30(brs, 1H), 5.02(ABq, J=9.0Hz, $\Delta\upsilon$ =270Hz), 4.89(s,1H), 4.52(d,1H, J=8.1Hz), 4.26(dd, 1H, J=8.1, 3.0Hz), 3.05(q, 1H, J=6.9Hz), 2.82(brs, 2H), 2.36(s, 3H), 2.28(m,1H), 1.93(brs, 2H), 1.29(d, 3H, J=6.9Hz), 1.14(s, 9H).

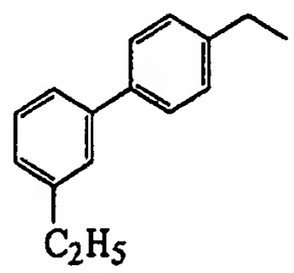
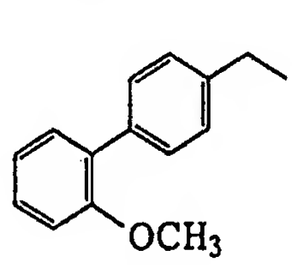
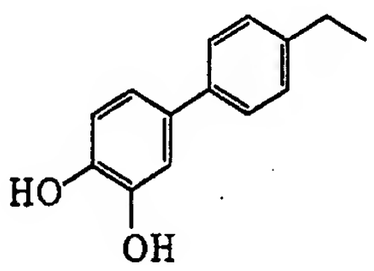
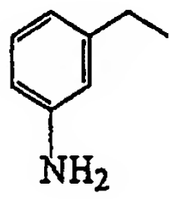
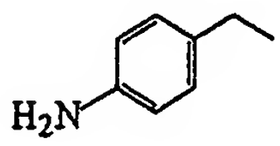
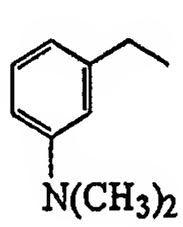
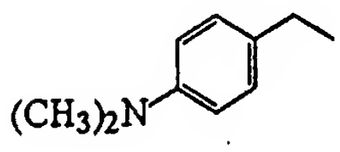
Examples 44 to 77

In the same manner as in the Example 43, the following compounds were prepared.

Example	R^1	R^2	m. p.(℃)
44		H	
45		H	
46		H	
47		H	
48		H	
49		H	
50		H	119.2 ~ 120.7
51		H	162.1 ~ 164.5
52		H	

Example	R^1	R^2	(℃)
53		H	
54		H	
55		H	
56		H	
57		H	
58		H	
59		H	132.7 ~ 134.3
60		H	129.5 ~ 131.3
61		H	

Example	R^1	R^2	m. p.(℃)
62		H	
63		H	
64		H	137.2 ~ 138.6
65		H	157 ~ 159
66		H	
67		H	
68		H	
69		H	
70		H	

Example	R^1	R^2	m. p.(℃)
71		H	
72		H	
73		H	175 ~ 177
74		H	119 ~ 123
75		H	
76		H	
77		H	185.2 ~ 186.7

Example 78. 10-(3'-phenoxypropoxy)-Ginkgolide B

To a solution of 50 ㎎ of Ginkgolide B in 5 *㎖* of tetrahydrofuran wasadded 16 ㎎ of potassium hydride followed by stirring, in an inert atmosphere, at room temperature for 5 minutes. To the mixture was then added 117 ㎎ of 3-phenoxypropyltrifluoromethanesulfonate, followed by stirring at room temperature for 4 hours.

The mixture was treated with 0.5 *㎖* of c- HCl at 0 ℃, diluted with 10 *㎖* of water and extracted with 50 *㎖* of ethylacetate. The solution was washed with 10 *㎖* of water and dried over anhydrous magnesium sulfate. After filtering off, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (elution solvent: chloroform / methanol = 99 / 1) to give 63 ㎎(95 %) of the desired compound.

^{1}H-NMR ($CDCl_3$) ; δ 7.31(t, 2H, J=7.8Hz), 7.02(t, 1H, J=7.8Hz), 6.92(d, 2H, J=7.8Hz), 5.95(s, 1H), 5.59(m, 1H), 5.43(brs, 1H), 4.78(m, 1H), 4.70(s, 1H), 4.66(d, 1H, J=8.1Hz), 4.35(dd, 1H, J=8.1, 3.0Hz), 4.10~3.82(m, 4H), 3.86(d, 1H, J=3.0Hz), 3.06(q, 1H, J=6.9Hz), 2.97(s, 1H), 2.25~1.80(m, 3H), 1.31(d, 3H, J=6.9Hz), 1.03(s, 9H).

Example 79. 10-(2'-phenylethoxy)-Ginkgolide B

To a solution of 50 ㎎ of Ginkgolide B in 5 *㎖* of tetrahydrofuran was added 16 ㎎ of potassium hydride followed by stirring, in an inert atmosphere, at room temperature for 5 minutes. To the mixture was then added 83 ㎎ of 2-phenyethylmethanesulfonate, followed by stirring at 70 ℃ for 4 hours.

The mixture was treated with 0.5 *㎖* of c- HCl at 0 ℃, diluted with 10 *㎖* of water and extracted with 50 *㎖* of ethylacetate. The solution was

washed with 10 *ml* of water and dried over anhydrous magnesium sulfate. After filtering off, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (elution solvent: chloroform / methanol = 99 / 1) to give 46 mg(73 %) of the desired compound.

^{1}H-NMR ($CDCl_3$) ; δ 7.30(m, 5H), 5.90(s, 1H), 5.27(d, 1H, *J*=3.9Hz), 4.89(m, 1H), 4.64(s, 1H), 4.54(d, 1H, *J*=7.8Hz), 4.16(dd, 1H, *J*=7.8, 3.0Hz), 3.80(m, 1H), 2.98(m, 3H), 2.13(dd, 1H, 13.6, 3Hz), 1.84(dd, 1H, 13.6, 3Hz), 1.79(m, 1H), 1.27(d, 3H, 6Hz), 1.05(s, 9H).

Example 80. 10-(3',4'.5'-trimethoxybenzoyloxy)-Ginkgolide B

To a solution of 50 mg of Ginkgolide B in 5 *ml* of pyridine was added 1 mg of *N*,*N*-dimethylaminopyridine and 95 mg of 3,4,5-trimethoxybenzoyl chloride, in an inert atmosphere, at room temperature. The mixture was stirred at room temperature for 4 hours.

The mixture was treated with 50 *ml* of 2N- HCl at 0 ℃, diluted with 10 *ml* of water and extracted with 150 *ml* of ethylacetate. The solution was washed with 20 *ml* of water and dried over anhydrous magnesium sulfate. After filtering off, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (elution solvent: chloroform / methanol = 99 / 1) to give 50 mg(68 %) of the desired compound.

^{1}H-NMR ($CDCl_3$) ; δ 7.33(s, 2H), 6.21(s, 1H), 6.15(s, 1H), 5.60(d, 1H, *J*=7.7Hz), 5.29(s, 1H), 4.65(d, 1H, *J*=7.2Hz), 4.40(d, 1H, *J*=6.9Hz), 4.12(q, 1H, *J*=3.0Hz), 3.90(d, 9H, *J*=9.0Hz), 3.10(q, 1H, *J*=6.9Hz), 2.37(m, 1H), 2.04(m, 2H), 1.28(d, 3H, *J*=6.9Hz), 1.04(s, 9H).

Example 81. 10-(4'-phenylbenzyloxy)-Ginkgolide B

To a solution of 50 ㎎ of Ginkgolide B in 5 *㎖* of tetrahydrofuran was added 16 ㎎ of potassium hydride followed by stirring, in an inert atmosphere, at room temperature for 5 minutes. To the mixture was then added 121 ㎎ of 4-phenylbenzyl iodide, followed by stirring at room temperature for 4 hours.

The mixture was treated with 0.5 *㎖* of c- HCl at 0 ℃, diluted with 10 *㎖* of water and extracted with 50 *㎖* of ethylacetate. The solution was washed with 10 *㎖* of water and dried over anhydrous magnesium sulfate. After filtering off, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (elution solvent: chloroform / methanal = 99 / 1) to give 57 ㎎(82 %) of the desired compound.

^{1}H-NMR ($CDCl_3$) ; δ 7.63(m, 4H), 7.42(m, 5H), 6.00(s, 1H), 5.34(brs, 1H), 5.09(ABq, 2H, J=9.3, $\Delta\upsilon$ =270Hz), 4.94(s, 1H), 4.55(d, 1H, J=7.8Hz), 4.31(dd, 1H, J=7.8, 2.7Hz), 3.06(q, 1H, J=6.9Hz), 2.98(s, 1H), 2.89(d, 1H, J=7.8, 2.7Hz), 2.29(m, 1H), 1.95(brs, 2H), 1.30(d, 3H, J=6.9Hz), 1.16(s, 9H)

Example 82. 10-piperonyloxy-Ginkgolide B

To a solution of 50 ㎎ of Ginkgolide B in 5 *㎖* of tetrahydrofuran was added 16 ㎎ of potassium hydride followed by stirring, in an inert atmosphere, at room temperature for 5 minutes. To the mixture was then added 108 ㎎ of piperonyl iodide, followed by stirring at room temperature for 4 hours.

The mixture was treated with 0.5 *㎖* of c-HCl at 0 ℃, diluted with 10 *㎖* of water and extracted with 50 *㎖* of ethylacetate. The solution was

washed with 10 *ml* of water and dried over anhydrous magnesium sulfate. After filtering off, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (elution solvent: chloroform / methanol = 99 / 1) to give 59 mg(89 %) of the desired compound.

^{1}H-NMR ($CDCl_3$) ; δ 6.84(d, 1H, J=3.0Hz), 6.83(d, 1H, J=9.0Hz), 6.82(dd,1H, J=9.0, 3.0Hz), 5.99(s, 2H), 5.98(s, 1H), 5.31(brs,1H), 4.94(ABq, 2H, J=9.0Hz, $\Delta\upsilon$ =258Hz), 4.87(s, 1H), 4.51(d, 1H, J=9.0Hz), 4.24(d, 1H, J=9.0, 3.0Hz), 3.22(s, 1H), 3.04(q, 1H, J=6.0Hz), 2.88(d, 1H, J=3.0Hz), 2.28(brd, 1H, J=6.0Hz), 1.93(s, 2H), 1.29(d, 3H, J=6.0Hz), 1.13(s, 9H).

Example 83. 10-(2',3',4',5',6',-pentafluorobenzyloxy)-Ginkgolide B

To a solution of 50 mg of Ginkgolide B in 5 *ml* of tetrahydrofuran wasadded 16 mg of potassium hydride followed by stirring, in an inert atmosphere, at room temperature for 5 minutes. To the mixture was then added 108 mg of α-bromo-2,3,4,5,6-pentafluorotoluene, followed by stirring at room temperature for 4 hours.

The mixture was treated with 0.5 *ml* of c- HCl at 0 ℃, diluted with 10 *ml* of water and extracted with 50 *ml* of ethylacetate. The solution was washed with 10 *ml* of water and dried over anhydrous magnesium sulfate. After filtering off, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (elution solvent: chloroform / methanol = 99 / 1) to give 53 mg(74 %) of the desired compound.

^{1}H-NMR ($CDCl_3$) ; δ 6.00(s, 1H), 5.36(brs, 1H), 5.22(ABq, 2H, J=10.8Hz, $\Delta\upsilon$ =243Hz), 4.92(s, 1H), 4.58(d, 1H, J=6.0Hz),

4.27(dd, 1H, J=6.0, 3.0Hz), 3.04(s, 1H), 3.02(brs, 1H), 2.78(brs, 1H), 2.27(d, 1H, J=9.0, 3.0Hz), 1.90(m, 2H), 1.29(d, 3H, J=6.0Hz), 1.10(s, 9H).

Example 84. 10-(3'-fluorobenzyloxy)-Ginkgolide B

To a solution of 50 ㎎ of Ginkgolide B in 5 ㎖ of tetrahydrofuran was added 16 ㎎ of potassium hydride followed by stirring, in an inert atmosphere, at room temperature for 5 minutes. To the mixture was then added 78 ㎎ of 3-fluorobenzyl bromide, followed by stirring at room temperature for 4 hours.

The mixture was treated with 0.5 ㎖ of c- HCl at 0 ℃, diluted with 10 ㎖ of water and extracted with 50 ㎖ of ethylacetate. The solution was washed with 10 ㎖ of water and dried over anhydrous magnesium sulfate. After filtering off, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (elution solvent: chloroform / methanol = 99 / 1) to give 52 ㎎(83 %) of the desired compound.

^{1}H-NMR ($CDCl_3$) ; δ 7.40(m, 1H), 7.10(m, 3H), 5.99(s, 1H), 5.34(s, 1H), 5.04(ABq, 2H, J=9.3Hz, $\Delta\upsilon$ =263Hz), 4.91(s, 1H), 4.54(d, 1H, J=7.8Hz), 4.26(d, 1H, J=7.8Hz), 3.05(m, 2H), 2.78(s, 1H), 2.30(d, 1H, J=7.5Hz), 1.94(s, 2H), 1.29(d, 3H, J=6.6Hz), 1.14(s, 9H).

Example 85. 10-(4'-fluorobenzyloxy)-Ginkgolide B

To a solution of 50 ㎎ of Ginkgolide B in 5 ㎖ of tetrahydrofuran was added 16 ㎎ of potassium hydride followed by stirring, in an inert atmosphere, at room temperature for 5 minutes. To the mixture was then added 78 ㎎ of 4-fluorobenzyl bromide, followed by stirring at room

temperature for 4 hours.

The mixture was treated with 0.5 *ml* of c- HCl at 0 ℃, diluted with 10 *ml* of water and extracted with 50 *ml* of ethylacetate. The solution was washed with 10 *ml* of water and dried over anhydrous magnesium sulfate. After filtering off, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (elution solvent: chloroform / methanol = 99 / 1) to give 53 ㎎(85 %) of the desired compound.

^{1}H-NMR ($CDCl_3$) ; δ 7.35(m, 2H), 7.10(m, 2H), 5.98(s, 1H), 5.30(brs, 1H), 5.01(ABq, 2H, J=9.6Hz, $\Delta\upsilon$ =267Hz), 4.90(s, 1H), 4.53(d,1H, J=7.8Hz), 4.25(d, 1H, J=7.8Hz), 3.04(q, 1H, J=6.9Hz),2.27(d, 1H, J=9.3Hz), 2.08(m, 1H), 1.93(m, 1H), 1.26(d, 3H,J=6.9Hz), 1.16(s, 9H).

Example 86. 10-(2',4'-difluorobenzyloxy)-Ginkgolide B

To a solution of 50 ㎎ of Ginkgolide B in 5 *ml* of tetrahydrofuran was added 16 ㎎ of potassium hydride followed by stirring, in an inert atmosphere, at room temperature for 5 minutes. To the mixture was then added 105 ㎎ of 2,4-difluorobenzyl iodide, followed by stirring at room temperature for 4 hours.

The mixture was treated with 0.5 *ml* of c- HCl at 0 ℃, diluted with 10 *ml* of water and extracted with 50 *ml* of ethylacetate. The solution was washed with 10 *ml* of water and dried over anhydrous magnesium sulfate. After filtering off, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (elution solvent: chloroform / methanol = 99 / 1) to give 45 ㎎(85 %) of the desired compound.

^{1}H-NMR ($CDCl_3$) ; δ 7.40(q, 1H, J=6.0Hz), 6.92(m, 2H), 5.32(d, 1H, J=3.0Hz), 5.10(ABq, 2H, J=9.9Hz, $\Delta\upsilon$ =196Hz),

4.91(s, 1H), 4.54(d, 1H, *J*=7.8Hz), 4.24(dd, 1H, *J*=7.8, 3.0Hz), 3.04(q, 1H, *J*=6.0Hz), 2.81(d, 1H, *J*=3.0Hz), 2.26(m, 1H), 1.90(m, 2H), 1.29(d, 3H, *J*=6.0Hz), 1.12(s, 9H).

Example 87. 10-(2'-fluorobenzyloxy)-Ginkgolide B

To a solution of 50 ㎎ of Ginkgolide B in 5 *㎖* of tetrahydrofuran was added 16 ㎎ of potassium hydride followed by stirring, in an inert atmosphere, at room temperature for 5 minutes. To the mixture was then added 78 ㎎ of 2-fluorobenzyl bromide, followed by stirring at room temperature for 4 hours.

The mixture was treated with 0.5 *㎖* of c- HCl at 0 ℃, diluted with 10 *㎖* of water and extracted with 50 *㎖* of ethylacetate. The solution was washed with 10 *㎖* of water and dried over anhydrous magnesium sulfate. After filtering off, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (elution solvent: chloroform / methanol = 99 / 1) to give 49 ㎎(79 %) of the desired compound.

^{1}H-NMR ($CDCl_3$) ; δ 7.40(brs, 2H), 7.19(m, 2H), 5.98(s, 1H), 5.31(s, 1H), 5.14(ABq, 2H, *J*=9.6Hz, $\Delta\upsilon$ =196Hz), 4.92(s, 1H), 4.54(d, 1H, *J*=7.8Hz), 4.26(brs, 1H), 3.05(m, 2H), 2.86(s, 1H), 2.25(m, 1H), 1.91(s, 2H), 1.29(d, 3H, *J*=6.4Hz), 1.10(s, 9H).

Example 88. 10-benzoyloxy-Ginkgolide B

To a solution of 50 ㎎ of Ginkgolide B in 5 *㎖* of pyridine was added 1 ㎎ of *N,N*-dimethylaminopyridine and 100 ㎎ of benzoyl chloride, in an inert atmosphere, at room temperature. The mixture stirred at room

temperature for 4 hours.

The mixture was treated with 50 *ml* of 2N HCl at 0 ℃, diluted with 20 *ml* of water and extracted with 150 *ml* of ethylacetate. The solution was washed with 10 *ml* of water and dried over anhydrous magnesium sulfate. After filtering off, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (elution solvent: chloroform / methanol = 99 / 1) to give 22 ㎎(35 %) of the desired compound.

^{1}H-NMR ($CDCl_3$) ; δ 8.05(d, 2H, *J*=7.8Hz), 7.63(t, 1H, *J*=7.5Hz), 7.50(t, 2H, *J*=7.5Hz), 6.27(s, 1H), 6.15(s, 1H), 5.64(d, 1H, *J*=3.6Hz), 4.65(d, 1H, *J*=7.2Hz), 4.31(brs, 1H), 3.10(q,1H, *J*=6.9Hz), 2.38(d, 1H, *J*=9.0Hz), 2.02(d, 2H, *J*=5.7Hz), 1.28(d, 3H, *J*=6.9Hz), 1.05(s, 9H).

Example 89. 1-benzoyloxy-Ginkgolide B

In the same manner as in the Example 88, the title compound was prepared(18 ㎎, 29 %).

^{1}H-NMR ($CDCl_3$) ; δ 7.93(d, 2H, *J*=7.8Hz), 7.62(t, 1H, *J*=7.5Hz), 7.93(t, 2H, *J*=7.5Hz), 6.02(s, 1H), 5.78(d, 1H, *J*=6.9Hz), 5.65(d, 1H, *J*=3.6Hz), 5.04(s, 1H), 4.76(d, 1H, *J*=6.9Hz), 3.21(q, 1H, *J*=7.2Hz), 2.38(dd, 1H, *J*=7.2, 3.0Hz), 2.00(m, 2H), 1.32(d, 3H, *J*=7.2Hz), 1.09(s, 9H)

Example 90. 10-benzenesulfonyloxy-Ginkgolide B

To a solution of 50 ㎎ of Ginkgolide B in 5 *ml* of pyridine was added 150 ㎎ of benzenesulfonyl chloride followed by stirring, in an inert atmosphere, at room temperature. The mixture stirred at room temperature for 4 hours.

The mixture was treated with 30 *ml* of 2N- HCl at 0 ℃, diluted with 20 *ml* of water and extracted with 150 *ml* of ethylacetate. The solution was washed with 10 *ml* of water and dried over anhydrous magnesium sulfate. After filtering off, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (elution solvent: chloroform / methanol = 99 / 1) to give 41 ㎎(62 %) of the desired compound.

^{1}H-NMR ($CDCl_3$) ; δ 8.02(d, 2H, J=6.0Hz), 7.76(t, 1H, J=6.0Hz), 7.63(t, 2H, J=6.0Hz), 6.05(s, 1H), 5.96(s, 1H), 5.45(d, 1H, J=3.0Hz), 4.56(d, 1H, J=7.5Hz), 4.04(dd, 1H, J=7.5Hz, 3.0Hz), 3.06(s, 1H), 2.91(q, 1H, J=6.0Hz), 2.75(s, 1H), 2.29(d, 1H, J=9.0Hz), 1.97(s, 2H), 1.25(d, 3H, J=6.0Hz), 1.15(s, 9H).

Example 91. 10-(3'-methoxybenzyloxy)-Ginkgolide B

To a solution of 50 ㎎ of Ginkgolide B in 5 *ml* of tetrahydrofuran was added 16 ㎎ of potassium hydride followed by stirring, in an inert atmosphere, at room temperature for 5 minutes. To the mixture was then added 102 ㎎ of 3-methoxybenzyl bromide, followed by stirring at room temperature for 4 hours.

The mixture was treated with 0.5 *ml* of c- HCl at 0 ℃, diluted with 10 *ml* of water and extracted with 50 *ml* of ethylacetate. The solution was washed with 10 *ml* of water and dried over anhydrous magnesium sulfate. After filtering off, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (elution solvent: chloroform / methanol = 99 / 1) to give 48 ㎎(75 %) of the desired compound.

^{1}H-NMR ($CDCl_3$) ; δ 7.33(t, 1H, J=7.8Hz), 6.93(d, 2H, J=7.8Hz), 6.87(s, 1H), 5.99(s, 1H), 5.32(brs, 1H), 5.04(ABq, 2H, J=9.3Hz, $\Delta\upsilon$

=267Hz), 4.90(s, 1H), 4.54(d, 1H, J=7.8Hz), 4.28(brd, 1H), 3.82(s, 3H), 3.05(q, 1H, J=6.9Hz), 2.87(brs, 2H), 2.29(m, 1H), 1.94(m, 2H), 1.30(d, 3H, J=6.9Hz), 1.14(s, 9H).

Example 92. 1,10-bis(2',4'-dichlorobenzyloxy)-Ginkgolide B

To a solution of 50 ㎎ of Ginkgolide B in 5 *㎖* of tetrahydrofuran was added 16 ㎎ of potassium hydride followed by stirring, in an inert atmosphere, at room temperature for 5 minutes. To the mixture was then added 260 ㎎ of 2,4-dichlorobenzyliodide, followed by stirring at room temperature for 4 hours.

The mixture was treated with 0.5 *㎖* of c- HCl at 0 ℃, diluted with 10 *㎖* of water and extracted with 50 *㎖* of ethylacetate. The solution was washed with 10 *㎖* of water and dried over anhydrous magnesium sulfate. After filtering off, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (elution solvent: chloroform / methanol = 99 / 1) to give 40 ㎎(45 %) of the desired compound.

^{1}H-NMR ($CDCl_3$) ; δ 7.21~6.88(m, 6H), 6.02(s, 1H), 5.64(d, 1H, J=3.6Hz), 5.02(ABq, 2H, J=10.5, $\Delta\upsilon$ =207Hz), 4.85(s, 1H), 4.59(d, 1H, J=13.5Hz), 4.43(ABq, 2H, J=6.3Hz, $\Delta\upsilon$ =168Hz), 3.94(d, 1H, J=13.5Hz), 3.30(q, 1H, J=6.9Hz), 2.93(s, 1H), 2.40~1.90(m, 3H), 1.32(d, 3H, J=6.9Hz), 1.13(s, 9H).

Example 93. 10-(3'-trifluoromethylbenzyloxy)-Ginkgolide B

To a solution of 50 ㎎ of Ginkgolide B in 5 *㎖* of tetrahydrofuran was added 16 ㎎ of potassium hydride followed by stirring, in an inert atmosphere, at room temperature for 5 minutes. To the mixture was then

added 99 ㎎ of 4-trifluoromethylbenzyl bromide, followed by stirring at room temperature for 4 hours.

The mixture was treated with 0.5 *㎖* of c- HCl at 0 ℃, diluted with 10 *㎖* of water and extracted with 50 *㎖* of ethylacetate. The solution was washed with 10 *㎖* of water and dried over anhydrous magnesium sulfate. After filtering off, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (elution solvent: chloroform / methanol = 99 / 1) to give 45 ㎎(65 %) of the desired compound.

^{1}H-NMR ($CDCl_3$) ; δ 7.67~7.58(m, 4H), 6.00(s, 1H), 5.34(brs, 1H), 5.12(ABq, J=9.9, $\Delta\upsilon$ =267Hz), 4.93(s, 1H), 4.55(d, 1H, J=7.8Hz), 4.26(dd, 1H, J=7.8, 2.4Hz), 3.05(q, 1H, J=6.9Hz), 2.86(s, 1H), 2.68(d, 1H, J=2.4Hz), 2.31(m, 1H), 1.94~1.90(m, 2H), 1.30(d, 3H, J=6.9Hz), 1.14(s, 9H).

Example 94. 10-(4'-trifluoromethylbenzyloxy)-Ginkgolide B

To a solution of 50 ㎎ of Ginkgolide B in 5 *㎖* of tetrahydrofuran was added 16 ㎎ of potassium hydride followed by stirring, in an inert atmosphere, at room temperature for 5 minutes. To the mixture was then added 99 ㎎ of 4-trifluoromethylbenzyl bromide, followed by stirring at room temperature for 4 hours.

The mixture was treated with 0.5 *㎖* of c- HCl at 0 ℃, diluted with 10 *㎖* of water and extracted with 50 *㎖* of ethylacetate. The solution was washed with 10 *㎖* of water and dried over anhydrous magnesium sulfate. After filtering off, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (elution solvent: chloroform / methanol = 99 / 1) to give 39 ㎎(58 %) of the desired compound.

^{1}H-NMR ($CDCl_3$) ; δ 7.70(d, 2H, J=7.8Hz), 7.49(d, 2H, J=7.8Hz), 6.01(s,

1H), 5.33(brs, 1H), 5.12(ABq, 2H, J=10.2, $\Delta\upsilon$ =279Hz), 4.92(s, 1H), 4.54(d, 1H, J=7.8Hz), 4.28(dd, 1H, J=7.8, 3.0Hz), 3.05(q, 1H, J=6.9Hz), 2.86(s, 1H), 2.69(d, 1H, J=3.0Hz), 2.31(m, 1H), 1.95~1.91(m, 2H), 1.27(d, 3H, J=6.9Hz), 1.15(s, 9H).

Example 95. 1,10-bis(4'-trifluoromethylbenzyloxy)-Ginkgolide B

To a solution of 50 mg of Ginkgolide B in 5 *ml* of tetrahydrofuran was added 16 mg of potassium hydride followed by stirring, in an inert atmosphere, at room temperature for 5 minutes. To the mixture was then added 198 mg of 4-trifluoromethylbenzylbromide, followed by stirring at room temperature for 4 hours.

The mixture was treated with 0.5 *ml* of c- HCl at 0 ℃, diluted with 10 *ml* of water and extracted with 50 *ml* of ethylacetate. The solution was washed with 10 *ml* of water and dried over anhydrous magnesium sulfate. After filtering off, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (elution solvent: chloroform / methanol = 99 / 1) to give 33 mg(38 %) of the desired compound.

^{1}H-NMR ($CDCl_3$) ; δ 7.41(d, 2H, J=8.1Hz), 7.24(s, 4H), 6.88(s, 1H), 6.03(s, 1H), 5.63(d, 1H, J=3.6Hz), 5.07(ABq, 2H, J=11.4, $\Delta\upsilon$ =270Hz), 4.88(s, 1H), 4.64(d, 1H, J=12.0Hz), 4.45(ABq, 2H, J=6.6, $\Delta\upsilon$ =162Hz), 4.15(d, 1H, J=12.0Hz), 3.21(q, 1H, J=7.2Hz), 2.95(s, 1H), 2.37(dd, 1H, J=13.2, 3.9Hz), 2.11(td, 1H, J=8.2, 3.9Hz), 1.97(dd, 1H, J=14.4, 3.9Hz), 1.33(d, 3H, J=7.2Hz), 1.13(s, 9H).

Example 96. 10-(3,5-dimethyl-2-pyridinyl)-methoxy-Ginkgolide B

To a solution of 2.0 g of Ginkgolide B in 50 *ml* of tetrahydrofuran was added 1.5g of 35 % potassium hydride followed by stirring, in an inert atmosphere, at room temperature for 5 minutes. To the mixture was then added 2.2g of 3,5-dimethyl-2-picolyl bromide and refluxed under heating with stirring for 1 hours.

The mixture was treated with 4 *ml* of 6N- HCl at 0 ℃, diluted with 10 *ml* of water and extracted with 50 *ml* of ethylacetate. The solution was washed with 10 *ml* of water and dried over anhydrous magnesium sulfate. After filtering off, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (elution solvent: chloroform / methanol = 99 / 1) to give 1.97 g(77 %) of the desired compound.

^{1}H-NMR ($CDCl_3$) ; δ 8.20(brs, 1H), 7.33(brs, 1H), 5.99(s, 1H), 5.63(brd, 1H), 5.14(ABq, 2H, *J*AB = 15Hz, $\Delta\upsilon$ =228Hz), 4.97(s, 1H), 4.64(d, 1H, *J* = 7.5Hz), 4.44(d, 1H, *J* = 7.5Hz), 3.07(q, 1H, *J* = 6.9Hz), 2.86(brs, 1H), 2.30(s, 3H), 2.17(s, 3H), 2.25~1.93(overlapping m, 3H), 1.30(d, 3H, *J* = 6.9Hz), 1.11(2, 9H).

Example 97. 10-(4-methoxy-3,5-dimethyl-2-pyridinyl)-methoxy-Ginkgolide B

To a solution of 100 ㎎ of Ginkgolide B in 8 *ml* of tetrahydrofuran was added 137 ㎎ of 35 % potassium hydride followed by stirring, in an inert atmosphere, at room temperature for 3 minutes. To the mixture was then added 65 ㎎ of 4-methoxy-3,5-dimethyl-2-picolyl chloride and refluxed under heating with stirring for 10 hours.

The mixture was treated with 0.5 *ml* of 6N- HCl at 0 ℃, diluted with

10 *ml* of water and extracted with 50 *ml* of ethylacetate. The solution was washed with 10 *ml* of water and dried over anhydrous magnesium sulfate. After filtering off, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (elution solvent: chloroform / methanol = 99 / 1) to give 76 mg(55 %) of the desired compound.

^{1}H-NMR ($CDCl_3$) ; δ 8.15(s, 1H), 8.07(d, 1H, J=4.2Hz), 6.40(s, 1H), 6.20(s, 1H), 5.41(brs, 2H), 5.09(ABq, 2H, JAB=14.4Hz, $\Delta\upsilon$ =146Hz), 4.63(d, 1H, J=7.5Hz), 4.16(d, 1H, J=4.2Hz), 3.75(s, 3H), 2.91(q, 1H J=7.2Hz), 2.20(s, 3H), 2.07(s, 3H), 2.14~1.80(m, 3H), 1.13(d, 3H, J=7.2Hz), 1.06(s, 9H).

Example 98. 10-(3,5-dimethyl-4-nitro-2-pyridinyl)-methoxy- Ginkgolide B

To a solution of 2.5g of Ginkgolide B in 50 *ml* of tetrahydrofuran was added 1.5 g of 35 % potassium hydride followed by stirring, in an inert atmosphere, at room temperature for 5 minutes. To the mixture was then added 2.0g of 3,5-dimethyl-4-nitro-2-picolyl chloride and refluxed under heating with stirring for 1 hour.

The mixture was treated with 4 *ml* of 6N- HCl at 0 ℃, diluted with 20 *ml* of saturated sodium bicarbonate solution and extracted with 100 *ml* of dichloromethane. The solution was washed with 10 *ml* of water and dried over anhydrous magnesium sulfate. After filtering off, the filtrate wasconcentrated under reduced pressure. The residue was subjected to chromatography on silica gel (elution solvent: chloroform / methanol = 99 / 1) to give 2.9 g(84 %) of the desired compound.

^{1}H-NMR ($CDCl_3$) ; δ 8.44(s, 1H), 7.65(d, 1H, J=4.5Hz), 6.00(s, 1H), 5.60(s, 1H), 5.22(ABq, 2H, JAB=13.8Hz, $\Delta\upsilon$ =231Hz),

4.99(s, 1H), 4.63(d, 1H, *J*=7.5Hz), 4.40(dd, 1H, *J*=7.8Hz, 4.5Hz), 3.05(q, 1H *J*=6.9Hz), 2.89(s,1H), 2.31(s, 3H), 2.14(s, 3H), 2.27~1.98(overlapping m, 3H), 1.30(d, 3H, *J*=6.9Hz), 1.11(s, 9H).

Example 99. 10-(2-pyridinyl)-methoxy-Ginkgolide B

In the same manner as in the Example 97, the title compound was prepared using 160 ㎎ of Ginkgolide B and 200 ㎎ of 2-picolylchloride(78 ㎎, 40 %).

Example 100. 10-(5-butyl-2-pyridinyl)-methoxy-Ginkgolide B

In the same manner as in the Example 98, the title compound was prepared using 120 ㎎ of Ginkgolide B and 200 ㎎ of 5-butyl-2-picolyl chloride (118 ㎎, 74 %).

^{1}H-NMR (DMSO-d_6) ; δ 8.37(s, 1H), 7.54(d, 1H, *J*=7.8Hz), 7.04(d, 1H, *J*=7.8Hz), 5.98(s, 1H), 5.60(brs, 1H), 5.20(ABq, 2H, *J*AB=12.6Hz, $\Delta\upsilon$ =262Hz), 4.92(s, 1H), 4.64(d, 1H, *J*=7.5Hz), 4.46(d, 1H, *J*=7.5Hz), 3.07(q, 1H, *J*=6.9Hz), 2.62(t, 2H, *J*=7.8Hz), 2.27~1.96(overlapping m, 3H), 1.60(m, 2H), 1.38(m, 2H), 1.30(d, 3H, *J*=6.9Hz), 1.10(s, 9H), 0.93(t, 3HJ, *J*=7.5Hz).

Example 101. 10-(2-pyridinyl)-ethoxy-Ginkgolide B

To a solution of 120 ㎎ of Ginkgolide B in 10 ㎖ of tetrahydrofuran was added 137 ㎎ of 35 % potassium hydride followed by stirring, in an inert atmosphere, at room temperature for 5 minutes. To the mixture was then

added 239 ㎎ of 2-(2-trifluoromethanesulfonyloxyethyl)-pyridine and refluxed under heating with stirring for 1 hour.

The mixture was treated with 0.5 *㎖* of 6N- HCl at 0 ℃, diluted with 10 *㎖* of water and extracted with 50 *㎖* of dichloromethane. The solution was washed with 10 *㎖* of water and dried over anhydrous magnesium sulfate. After filtering off, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (elution solvent: chloroform / methanol = 99 / 1) to give 117 ㎎(78 %) of the desired compound.

^{1}H-NMR ($CDCl_3$) ; δ 8.49(brd, 1H), 7.71(td, 1H, *J*=7.5Hz, 1.5Hz), 7.27~7.18(m, 2H), 5.89(s, 1H), 5.58(brs, 1H), 4.66(d, 1H, *J*=7.5Hz), 4.63(s, 1H), 4.57(m, 1H), 4.26(d, 1H, *J*=7.5Hz), 3.92(m, 1H), 3.09~2.99(overlapping m, 3H), 2.91(s, 1H), 2.23~1.89(overlapping m, 3H), 1.27(d, 3H, *J*=6.9Hz), 1.04(s, 9H).

Example 102. 10-(2-quinolinyl)-methoxy-Ginkgolide B

In the same manner as in the Example 101, the title compound was prepared using 55 ㎎ of Ginkgolide B and 70 ㎎ of 2-(iodomethyl)-quinoline (41 ㎎, 55 %).

^{1}H-NMR ($CDCl_3$) ; δ 8.43(d, 1H, *J*=8.7Hz), 8.05~8.00(m, 2H), 7.95(d, 1H, *J*=4.8Hz), 7.83(t, 1H, *J*=7.8Hz), 7.47(t, 1H, *J*=7.8Hz), 7.49(d, 1H, *J*=8.7Hz), 6.47(brs, 1H), 6.22(s, 1H), 5.48(brd, 1H), 5.44(s, 1H), 5.35(ABq, 2H, $\Delta\upsilon$ = 146Hz, *J*=15.0Hz), 4.74(d, 1H, *J*=7.5Hz), 4.32(dd, 1H, *J*=7.5Hz, 4.8Hz), 2.89(q, 1H, *J*=6.9Hz), 2.30~1.70(overlapping m, 3H), 1.13(d, 3H, *J*=6.9Hz), 1.07(s,

9H).

Example 103. 10-(3,5-dimethyl-4-amino-2-pyridinyl)-methoxy- Ginkgolide B

To a mixture of 300 mg of 10-(3,5-dimethyl-4-nitro-2-pyridinyl)-methoxy-Ginkgolide B obtained in Example 98, 1 *ml* of c-HCl, 8 *ml* of tetrahydrofuran and 4 *ml* of water was added 233 mg of Zn with stirring at room temperature.

The mixture was stirred at room temperature for 1 hour, after filtering off, the filtrate was neutralized with 5 *ml* of saturated sodiumcarbonate solution, and extracted with 50 *ml* of ethylacetate.

The solution was dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was crystallized from ethyl ether to give 199 mg(70 %) of the desired compound.

^{1}H-NMR (CD_3OD) ; δ 7.79(s, 1H), 6.11(s, 1H), 5.47(brs, 1H), 5.29(s, 1H), 5.10(ABq, 2H, $\Delta\upsilon$ =176Hz, *J*AB=20.3Hz), 4.55(d, 1H, *J*=7.5Hz), 4.36(d, 1H, *J*=7.5Hz), 3.05(q, 1H, *J*=7.2Hz), 2.11(s, 3H), 1.99(s, 3H), 2.15~1.98(overlapping m, 3H), 1.24(d, 3H, *J*=7.2Hz), 1.21(s, 1H).

Example 104. 10-(3,5-dimethyl-4-hydroxyamino-2-pyridinyl)-methoxy-Ginkgolide B

To a mixture of 150 mg of 10-(3,5-dimethyl-4-nitro-2-pyridinyl)-methoxy-Ginkgolide B obtained in Example 98 in 3 *ml* of tetrahydrofuran and 3 *ml* of water, was added 106 mg of Zn and 22 mg of NH_4Cl followed by stirring at room temperature.

The mixture was stirred at room temperature for 1 hour. After filtering off, the filtrate was extracted with 10 *ml* of ethylacetate.

The solution was dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was crystallized from ethyl ether to give 103 ㎎(70 %) of the desired compound.

^{1}H-NMR (CD_3OD) ; δ 7.93(s, 1H), 6.12(s, 1H), 5.49(s, 1H), 5.31(s, 1H), 5.18(ABq, 2H, $\Delta\upsilon$ =176Hz, J=13.8Hz), 4.56(d, 1H, J=7.8Hz), 4.36(d, 1H, J=7.8Hz), 3.05(q, 1H, J=7.2Hz), 2.30(s, 3H), 2.13(s, 3H), 2.30~1.90(overlapping m, 3H), 1.23(d, 3H, J=7.2Hz), 1.12(s, 9H).

Example 105. 10-(4-benzoylamino-3,5-dimethyl-2-pyridinyl)-methoxy-Ginkgolide B

To a solution of 30 ㎎ of 10-(3,5-dimethyl-4- amino-2-pyridinyl) -methoxy-Ginkgolide B obtained in Example 103 in 3 ㎖ of tetrahydrofuran was added 12.5㎕ of benzoyl chloride followed by stirring at room temperature, followed by stirring at room temperature for 24 hours. The solution was concentrated and subjected to chromatography on silica gel to give 16 ㎎(45 %) of the desired compound.

^{1}H-NMR (CD_3Cl) ; δ 8.31(s, 1H), 7.94(d, 2H, J=7.2Hz), 7.62(t, 1H, J=7.8Hz), 7.60(brs, 1H), 7.54(t, 1H, J=7.8Hz), 5.99(s, 1H), 5.65(brs, 1H), 5.21(ABq, 2H, $\Delta\upsilon$ = 236Hz, JAB=13.5Hz), 4.99(s, 1H), 4.65(d, 1H, J=7.5Hz), 4.45(d, 1H, J=7.5Hz), 3.07(q, 1H, J=6.9Hz), 2.92(s, 1H), 2.270(s, 3H), 2.11(s, 3H), 2.30 ~1.90(overlapping m,3H), 1.29(d, 3H, J=6.9Hz), 1.11(s, 9H).

Example 106. 10-(4-*N*-benzoyl-*N*-hydroxyamino-3,5-dimethyl-2-pyridinyl)-methoxy Ginkgolide B

To a mixture of 20 ㎎ of 10-(3,5-dimethyl-4-hydroxyamino -2-pyridinyl) -methoxy-Ginkgolide B obtained in Example 104 in 2 *㎖* of ethylacetate and 2 *㎖* of saturated sodium carbonate solution was added 8.1-*㎕* of benzoyl chloride by stirring at room temperature. After 3 hours stirring at room temperature, the mixture was extracted with 9 *㎖* of dichloromethane. The solution was dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was subjected to chromatography on silica gel to give 17 ㎎(70 %) of the desired compound.

Example 107. 10-(6-chloro-3-pyridinyl)-methoxy-Ginkgolide B

In the same manner as in the Example 98, the title compound was prepared using 115 ㎎ of Ginkgolide B and 168 ㎎ of 6-chloro-3-picolyl chloride (87 ㎎, 59 %).

^{1}H-NMR (DMSO-d_6) ; δ 8.40(d, 1H, J=2.1Hz), 7.84(dd, 1H, J=8.3, 2.4Hz), 7.50(d, 1H, J=8.4Hz), 6.41(s, 1H), 6.15(s, 1H), 5.61(d, 1H, J=4.8Hz), 5.34(brs, 1H), 5.21(s, 1H), 5.04(ABq, 2H, JAB=12.3Hz, $\Delta\upsilon$ =192.3Hz), 4.60(d, 1H, J=6.6Hz), 4.18(t, 1H, J=5.7Hz), 2.88(q, 1H, J=7.2Hz), 2.15~2.07(m, 1H), 1.90~1.65(m, 2H), 1.12(d, 3H, J=7.2Hz), 0.99(s, 9H).

Example 108. 10-(3-pyridinyl)-methoxy-Ginkgolide B

In the same manner as in the Example 98, the title compound was prepared using 200 ㎎ of Ginkgolide B and 250 ㎎ of 3-picolyl chloride (164 ㎎, 68 %).

^{1}H-NMR (DMSO-d_6) ; δ 8.57(d, 1H, J=1.2Hz), 8.50(dd, 1H, J=4.7, 1.2Hz), 7.78(brd, 1H, J=7.8Hz), 7.38(dd, 1H, J=7.8, 4.8Hz), 6.42(s, 1H), 6.15(s, 1H), 5.38(d, 1H, J=5.4Hz), 5.33(d, 1H, J=3.3Hz), 5.23(s, 1H), 5.05(ABq, 2H, JAB=12.3Hz, $\Delta\upsilon$ =199.5Hz), 4.60(d, 1H, J=6.6Hz), 4.19(t, 1H, J=5.7Hz), 2.88(q, 1H, J=7.2Hz), 2.15~1.70(m, 3H), 1.12(d, 3H, J=7.2Hz), 0.99(s, 9H).

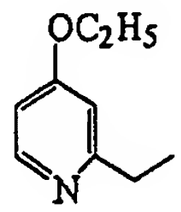
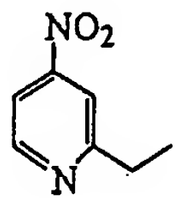
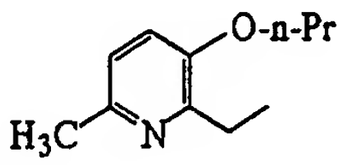
Example 109. 10-(4-pyridinyl)-methoxy-Ginkgolide B

In the same manner as in the Example 98, the titile compound was prepared using 200 ㎎ of Ginkgolide B and 240 ㎎ of 4-picolyl chloride (109 ㎎, 45 %).

^{1}H-NMR (DMSO-d_6) ; δ 8.52(d, 2H, J=5.4Hz), 8.35(d, 2H, J=5.4Hz), 6.42(s, 1H), 6.16(s, 1H), 5.74(d, 1H, J=5.1Hz), 5.40(d, 1H, J=3.6Hz), 5.22(s, 1H), 5.08(ABq, 2H, JAB=13.5Hz, $\Delta\upsilon$ =209Hz), 4.61(d, 1H, J=6.6Hz), 4.21(t, 1H, J=5.6Hz), 2.89(q, 1H, J=6.9Hz), 2.20~1.70(m, 3H), 1.12(d, 3H, J=6.9Hz), 0.99(s, 9H).

Example 110 to 112.

In the same manner as in the Example 96, the following compounds were prepared.

Example	R^1	R^2	m. p.(℃)
110		H	
111		H	
112		H	

Example113.10-(2-(4-hydroxyaminopyridinyl)-methoxy) -GinkgolideB

In the same manner as in the Example 104, the title compound was prepared using 10-(4-nitro-2-pyridinyl)-methoxy-Ginkgolide B obtained in Example 111 (85 %).

Example 114.10-(2-(5-(2-methoxyethoxymethoxy))- pyridinyl)-methoxy-Ginkgolide B

In the same manner as in the Example 96, the title compound was prepared using Ginkgolide B and 5-(2-methoxyethoxymethoxy)-2-picolyl bromide or mesylate of 5-(2-methoxyethoxymethoxy)-2-pyridyl carbinol. (76 %)

Example 115. 10-(2-(5-hydroxypyridinyl)-methoxy)-Ginkgolide B

To a solution of 250 mg of the compound obtained in Example 114 in 3 *ml* of tetrahydrofuran was added 1 *ml* of c-HCl followed by stirring at room

temperature. After 2 hours stirring at room temperature, the mixture was concentrated under reduced pressure.

The residue was subjected to chromatography on silica gel to give 185 mg(89 %) of the desired compound.

Example 116. 10-(2'-bromoethoxy)-Ginkgolide B

To a solution of 50 mg of Ginkgolide B in 5 *ml* of tetrahydrofuran was added 16 mg of potassium hydride followed by stirring, in an inert atmosphere, at room temperature for 5 minutes. To the mixture was then added 91 mg of 2-bromoethyltrifluoromethanesulfonate stirred at room temperature for 1 hour.

The mixture was treated with 0.5 *ml* of c-HCl at 0 ℃, diluted with 10 *ml* of water and extracted with 50 *ml* of dichloromethane. The solution was washed with 10 *ml* of water and dried over anhydrous magnesium sulfate. After filtering off, the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (elution solvent: chloroform / methanol = 99 / 1) to give 61 mg(98 %) of the desired compound.

^{1}H-NMR (DMSO) ; δ 6.43(s, 1H), 6.13(s, 1H), 5.34(d, 1H, J=3.0Hz), 5.13(s, 1H), 5.03(d, 1H, J=6.0Hz), 4.61(d, 1H, J=6.0Hz), 4.20(dt, 2H, J=9.0, 4.5Hz, $\Delta\upsilon$ =225Hz), 4.12(t, 1H, J=6.0Hz), 3.71(m, 2H), 2.85(q, 1H, J=6.9Hz), 2.14(dd, 1H, J=13.5, 3.6Hz), 1.94(m, 1H), 1.72(dd, 1H, J=13.5, 3.6Hz), 1.12(d, 1H, J=6.9Hz), 1.02(s, 9H).

Example 117. 10-(2'-iodoethoxy)-Ginkgolide B

To a solution of 1.30g of 10-(2'-bromoethoxy)-Ginkgolide B obtained

in Example 116 in 20 *ml* of anhydrous acetone was added 0.44g of sodium iodide followed by stirring at room temperature.

The mixture was stirred at room temperature for 15 hours. After filtering off, the filtrate was concentrated under reduced pressure. The residue was dissolved in 100 *ml* of ethyl ether, washed with 30 *ml* of 5 % sodium bisulfite solution, dried over anhydrous magnesium sulfate, filtered and concentrated to give 1.20 g(86 %) of the desired compound.

^{1}H-NMR ($CDCl_3$) ; δ 5.98(s, 1H), 5.50(d, 1H, *J*=3.0Hz), 4.80(s, 1H), 4.64(d, 1H, *J*=6.0Hz), 4.30(dd, 1H, *J*=6.0 and 3.0Hz), 4.29(m, 2H), 3.38(t, 2H, *J*=6.0Hz), 3.30(d, 1H,*J*=3.0Hz), 3.12(s, 1H), 3.03(q, 1H, *J*=6.0Hz), 2.33(dd, 1H, *J*=13.5 and 4.5Hz), 2.16(td, 1H, *J*=13.5 and 3.0Hz), 1.93(dd, 1H, *J*=13.5 and 4.5Hz), 1.29(d, 3H, *J*=6.0Hz), 1.11(s, 9H).

Example 118. 10-(2'-(1"-piperidinyl)-ethoxy)-Ginkgolide B

100 mg of 10-(2'-iodoethoxy)-Ginkgolide B obtained in Example 117 was dissolved in 2 *ml* of piperidine, and stirred at room temparature for 1 hour. The excess piperidine was removed under reduced pressure. The residue was subjected to chromatography on silica gel to give 57 mg(62 %) of the desired compound.

^{1}H-NMR ($CDCl_3$) ; δ 5.92(s, 1H), 5.52(d, 1H, *J*=3.0Hz), 4.72(s, 1H), 4.57(d, 1H, *J*=6.0Hz), 4.23(d, 1H, *J*=6.0Hz) 4.09(m,2H), 3.04(q, 1H, *J*=6.0Hz), 2.67(m, 3H), 2.28(m, 4H), 1.99(m, 2H), 1.64(m, 4H), 1.48(m, 2H), 1.29(d, 3H, *J*=6.0Hz), 1.08(s, 9H).

Example 119. 10-(2'-(1"-morpholinyl)-ethoxy)-Ginkgolide B

In the same manner as in the Example 118, the title compound was prepared using morpholine (75 %).

^{1}H-NMR ($CDCl_3$) ; δ 7.01(s, 1H), 5.94(s, 1H), 5.48(d, 1H, J=3.0Hz), 4.74(s, 1`H), 4.57(d, 1H, J=7.5Hz), 4.21(d, 1H, J=7.5Hz), 4.14(ABq, 2H, J=8.1Hz, $\Delta\upsilon$ =3.24Hz), 3.78(m, 4H), 3.07(m, 2H), 2.73(m, 3H), 2.46(m, 4H), 1.97(m, 2H), 1.20(d, 3H, J=7.2Hz), 1.10(s, 9H).

Example 120. 10-(2'-(1"-(1",2",4"-triazolyl)-ethoxy))-Ginkgolide B

To a stirred solution of 100 mg of 10-(2'-bromoethoxy)- Ginkgolide B obtained in Example 116 in 1.5 *ml* of dimethylsulfoxide was added 96 mg of 1,2,4-sodiumtriazole at room temperature.

The mixture was stirred at 80 ℃ for 2 hours, cooled to room temperature, diluted with 10 *ml* of water and extracted with 50 *ml* of ethylacetate. The solution was dried over anhydrous magnesium sulfate, filtered, concentrated under reduced pressure. The residue was subjected to chromatography on silica gel to give 72 mg(74 %) of the desired compound.

^{1}H-NMR (DMSO) ; δ 8.37(s, 1H), 7.98(s, 1H), 6.40(brs, 1H), 6.07(s, 1H), 5.83(brs, 1H), 5.32(d, 1H, J=3.0Hz), 4.97(s, 1H), 4.63(d, 1H, J=7.2Hz), 4.55(m, 2H), 4.35(m, 1H), 4.12(brs, 1H), 3.75(t, 1H, J=8.2Hz), 2.83(q, 1H, J=6.8Hz), 1.90(m, 1H), 1.60(m, 2H), 1.12(d, 3H, J=6.8Hz), 0.98(s, 9H).

Example 121. 10-(2'-(1"-piperazinyl)-ethoxy)-Ginkgolide B

To a stirred solution of 100 mg of 10-(2'-iodoethoxy)- Ginkgolide B obtained in Example 117 in 5 *ml* of pyridine was added 300 mg of piperazine

at room temperature. The mixture was stirred at room temperature for 3 hours, concentrated, diluted with 30 *ml* of saturated sodiumbicarbonate solution and extrated with 50 *ml* of ethylacetate. The solution was dried over anhydrous magnesium sulfate, filtaed, and concentrated under reduced pressure. The residue was subjected to chromatography on silica gel to give 62 mg(67 %) of the desired compound.

^{1}H-NMR (DMSO) ; δ 6.87(brs, 1H), 6.37(s, 1H), 5.30(d, 1H, 3.0Hz), 5.11(s, 1H), 4.55(d, 1H, 7.5Hz), 4.07(d, 1H, 7.5Hz), 3.99(m, 2H), 2.82(q, 1H, *J*=6.9Hz), 2.72(m, 4H), 2.50(m, 2H), 2.22(m, 5H), 1.98(td, 1H, *J*=13.0 and 3.0Hz), 1.76(dd, 1H, *J*=13.0 and 3.0Hz), 1.10(d, 3H, *J*=6.9Hz), 1.00(s, 9H).

Example 122. 10-(2'-(1"-pyrrolidinyl)-ethoxy)-Ginkgolide B

In the same manner as in the Example 118, the title compound was prepared using pyrrolidine (75 %).

^{1}H-NMR ($CDCl_3$) ; δ 5.92(s, 1H), 5.50(d, 1H, *J*=3.0Hz), 4.73(s, 1H), 4.60(t,1H, *J*=9.2Hz), 4.53(d, 1H, *J*=7.5Hz), 4.21(d, 1H, *J*=7.5Hz), 3.60(m, 1H), 3.04(q, 1H, *J*=6.0Hz), 2.92(m, 1H), 2.70(m, 2H), 2.45(m, 3H), 2.25(dd, 1H, *J*=13.0 and 3.0Hz), 2.00(m, 2H), 1.80(brs, 4H), 1.28(d, 3H, *J*=6.0Hz), 1.10(s, 9H).

Compounds which have PAF-antagonistic activity may be used for the treatment and prophylaxis of diseases mediated or effected by PAF.

Typical diseases for which the inventive compounds may be used as a therapeutic and prophylactic agent include allergic diseases, asthma,

thrombosis, cerebral apoplexy(cerebral hemorrhage, cerebral thrombosis), myocardial infarction(angina pectoris), human disseminated intravascular coagulation syndrome(DIC), thrombophlebitis, glomerular hepatitis, anaphylatic shock, hemorrhagic shock, septic shock, endotoxin shock, rheumatoid arthritis, osteoarthritis, edema, inflammation, cardiovascular disorder, adult respiratory distress syndrome, immune regulation, gastric ulceration, transplant rejection, psoriasis, allergic dermatitis, urticaria, multiple sclerosis, and other conditions in which PAF is implicated.

The inventive ginkgolide B derivatives have potent PAF-antagonistic activity. Accordingly, the new ginkgolide B derivatives may be used in pharmaceutical composition comprising a pharmaceutically effective amount of one of the compounds defined above and a pharmaceutically acceptable carrier. The compounds are effective for the therapy and prophylaxis of all diseases mediated or effected by PAF.

The inventive compounds are particularly useful as an anti-allergic agents, an anti-asthmatic agents, an anti-psoriasis agents, an anti-anaphylactic shock agents, an anti-septic shock agents, an anti-bowel necrosis agents, an adult respiratory distress syndrome agents and anti-transplant rejection agents.

Compounds of formula(I) may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles.

The term parenteral as used herein includes subcutaneous injections, intravenous injection, intramuscular injection, intrasternal injection or infusion techniques.

The dosage employed depends on the type of disease, the degree of

symptom and age. The dosage levels of the compound in the above-indicated compositions may, of course, be varied and may conveniently be between about 0.1 % to about 95 % of the weight the unit.

When these compounds are administered orally, a dose of 1~50 wt.% is particulary preferred.

For parenteral administration, a dose of 0.1~20 wt.% is particulary preferred be benefitial.

Pharmaceutical compositions containing compounds of formula(I) may be in any form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispensable powders or granules, emulsion, hard or soft capsules, syrups or elixirs.

The tablets, capsules and the like may also contain a binder, such as lactose, saccharose, sorbitol, manitol, starch, amylopectin, cellulose or gelatin; excipients, such as dicalcium phosphate; a disintegrating agent, such as corn starch or potato starch; a lubricant, such as magnesium stearate, calcium stearate, sodium stearylfumalate or polyethylenglycol wax. When the dosage unit form is a capsule, it may further contain, in addition to the type of materials described above, a liquid carrier, such as a fatty oil.

These active compounds of formula(I) may also be administered parenterally. A solution or suspension of the active compounds may be prepared in water, optionally mixed with stabilizer or buffering agents. The dosages for parenteral administration are 0.1~10 wt.% ; and preferably administered as ampule or vial type.

Dosage levels of about 2 ㎎ to about 1,000 ㎎(70 ㎏ of body weight, adult) per day are particularly useful for the prevention or treatment of allergic bronchial disease and allergic rheumatoid arthritis. For

intravenous injection for treating these conditions, dosage levels of about 1 mg to about 10 mg are particularly preferred.

The compound of the present invention may also be administered directly to the airways, for example, in the form of an aerosol or inhalation by nebulizer, for the treatment of allergic bronchial hypereactivity. Dosage unit forms will generally contain between about 0.1 mg to about 50 mg of theactive ingredient.

Accordingly, the present invention provides pharmaceutical compositions comprising a pharmaceutically effective amount of a compound of formula(I) and a pharmaceutically acceptable carrier. The present invention also provides the pharmaceutical uses of these compounds and compositions, especially for treatment of allergic diseases and inflammatory diseases in humans.

The following examples illustrate the typical pharmaceutical composition. In each case, the active ingredient represents a compounds of formula(I), which may be substituted by any pharmaceutically effective amount of another compound of general formula(I).

[pharmaceutical compositions]

Example 1 : Orally administration(Tablet)

Composition	mg/Tablet	mg/Tablet
Active Ingredient	100	500
Lactose	122	113
Corn starch/water	30	40
Corn starch	45	40
Magnesium stearate	3	7
Total	300	700

Example 2 : Parenteral administration

Composition	mg/vial	mg/vial
sterile active ingredient powder	100	500

※ Sterile water may be added to the above composition for intravenous injection.

The compounds of this invention were tested for pharmacological activity as described in the following pharmacology examples.

Pharmacology Example 1: PAF-induced rabbit platelet aggregation.

Blood was collected from the ear artery of a male New Zealand white rabbit and mixed with 3.8 % sodium citrate in a 9:1 volume ratio. Platelet rich plasma(PRP) was obtained by centrifugation of blood at 150 g for 10 min at room temperature. The number of platelets was adjusted to 3 x 10^8 platelets/*ml* with platelet poor plasma. Platelet aggregation was monitored by continuous recording of light transmission in a dual-channel aggregometer(Chrono-Log 560-VS) coupled with a two channel recorder(Chrono-Log 707). Stirred PRP was treated with various concentration of test compounds or vehicle(0.5 % DMSO) for 2 min and then PAF(5×10^{-9} M) was added to induce platelet aggregation.

Inhibition values were calculated by comparing the extent of aggregation obtainted in the presence of the vehicle alone(0.5 % DMSO) and in the presence of a test compound. Log concentration-response curves were generated and the IC_{50} values were determined by regression analysis.

Table 1 lists results from this assay for inhibition of PAF-induced rabbit platelet aggregation for illustrative examples of the compounds of this invention.

Table 1 : Results for inhibition of PAF-induced rabbit platelet aggregation

Example	IC_{50}(M)
Ginkgolide B	2.58×10^{-7}
Example 1	6.88×10^{-8}
Example 2	7.21×10^{-8}
Example 3	9.47×10^{-8}
Example 5	5.01×10^{-8}
Example 11	1.01×10^{-7}
Example 14	8.58×10^{-8}
Example 15	6.21×10^{-8}
Example 24	4.21×10^{-8}
Example 25	5.71×10^{-8}
Example 27	6.21×10^{-8}
Example 28	3.71×10^{-8}
Example 30	1.21×10^{-7}
Example 31	7.81×10^{-8}
Example 32	6.51×10^{-8}
Example 35	1.01×10^{-7}
Example 41	7.41×10^{-8}
Example 42	4.43×10^{-8}
Example 43	4.67×10^{-8}
Example 44	8.31×10^{-8}
Example 63	6.27×10^{-8}

Example 75	1.16×10^{-7}
Example 78	1.59×10^{-7}
Example 79	1.17×10^{-7}
Example 80	1.14×10^{-7}
Example 81	5.21×10^{-8}
Example 82	5.07×10^{-8}
Example 83	7.17×10^{-8}
Example 84	6.80×10^{-8}
Example 85	3.21×10^{-8}
Example 86	5.01×10^{-8}
Example 87	1.07×10^{-7}
Example 88	4.82×10^{-8}
Example 89	6.21×10^{-8}
Example 90	8.21×10^{-8}
Example 91	9.31×10^{-8}
Example 92	1.02×10^{-7}
Example 93	7.31×10^{-8}
Example 94	1.21×10^{-7}
Example 95	8.71×10^{-8}
Example 96	2.45×10^{-8}
Example 97	3.89×10^{-8}
Example 98	1.31×10^{-7}
Example 99	3.07×10^{-8}

Example 100	5.21×10^{-8}
Example 101	1.02×10^{-7}
Example 102	1.31×10^{-7}
Example 103	8.77×10^{-8}
Example 104	1.10×10^{-7}
Example 105	3.25×10^{-8}
Example 106	4.71×10^{-8}
Example 107	1.57×10^{-7}
Example 108	1.34×10^{-7}
Example 109	1.22×10^{-7}
Example 110	1.57×10^{-7}
Example 111	1.07×10^{-7}
Example 112	1.24×10^{-7}
Example 113	1.11×10^{-7}
Example 114	1.39×10^{-7}
Example 115	1.52×10^{-7}
Example 116	1.13×10^{-7}
Example 117	5.34×10^{-8}
Example 118	4.71×10^{-8}
Example 119	5.41×10^{-8}
Example 120	6.21×10^{-8}
Example 121	5.71×10^{-8}
Example 122	5.61×10^{-8}

Pharmacology Example 2: PAF-induced bronchoconstriction

All experiments utilized male guinea pigs(Hartley strain), weighing 350 to 450g, that were anesthetized with ethyl carbamate(1.5 g/kg, i.p.). An intratracheal cannula was inserted into trachea and indwelling catheters were inserted into the right carotid artery and left jugular vein. The animals were ventilated with a small animal respirator(UGO BASILE 7025, 70 breaths/min, 1㎖/stroke/100g). To monitor dead or not, mean arterial pressure was measured continuously with a pressure transducer(Physiological Pressure Transducer, MICRON INSTRUMENT MP-15) connected to an amplifier(COULBOURN INSTRUMENT S72-25) and recorder(COULBOURN INSTRUMENT R14-18). The rate of bronchoconstriction was measured as an increase in lung overflow with a bronchospasm transducer(UGO BASILE 7020) from a side arm off the tracheal cannula, and expressed as a percnetage of maximum bronchoconstriction obtained by clamping off the tracheal cannular. Test compounds or vehicle(0.5 % DMSO) were administered throμgh the cannula into the jugular vein and PAF(100ng/kg, i.v.) was administered. Bronchoconstriction response was compared to that obtained with control group treated with vehicle. Percent inhibition was calculated for each dose. Log dose-response curves were generated and the ID_{50} values were determined by regression analysis, and the results are presented in table 2.

Table 2 : Results for inhibition of PAF-induced bronchoconstriction in the guinea pig.

Example	Dose(㎎/㎏)	Inhibition(%)	ID_{50}(㎎/㎏)
Ginkgolide B	2.00	100	0.60
	1.00	64	
	0.50	38	
96	0.04	96	0.023
	0.02	26	
	0.01	17	

Pharmacology Example 3: Ag-induced bronchoconstriction

All experiments utilized male guinea pigs(Hartley strain), weighing 350 to 500g. The animal was passively sensitized with rabbit anti-chicken egg albumin(1.3 ㎎/㎏), 17~24 hrs before ovalbumin challenge. Passively sensitized animals were anesthetized with ethyl carbamate(1.5g/㎏, i.p.). An intratracheal cannula was inserted into trachea and indwelling catheters were inserted into the right carotid artery and left jugular vein. The animals were ventilated with a small animal respirator(UGO BASILE 7025, 70 breaths/min, 1 ㎖/stroke/100 g). To monitor dead or not, mean arterial pressure was measured continuously with a pressure transducer(Physiological Pressure Transducer, MICRON INSTRUMENT MP-15) connected to an amplifier(COULBOURN INSTRUMENT S72-25) and recorder(COULBOURN INSTRUMENT R14-18). The rate of bronchoconstriction was measured as an increase in lung overflow with a bronchospasm transducer(UGO BASILE 7020) from a side arm off the

tracheal cannula, and expressed as a percentage of maximum bronchoconstriction obtained by clamping off the tracheal cannular. Test compounds or vehicle(0.5 % DMSO) were administered through the cannula into the jugular vein and ovalbumin(1.0 ㎎/㎏, i.v.) was admnistered 10 minutes later. Bronchoconstriction response was compared to that obtained with control group treatd with vehicle. Percent inhibition was calculated for each dose. If nessary, log dose-response curves were generated and the ID_{50} values were determined by regression analysis. The results are presented in the following talbe 3.

Table 3 : Results for inhibition of Ag-induced bronchoconstriction in the guinea pig.

Example	Dose(㎎/㎏)	% inhibition	ID_{50}(㎎/㎏)
Ginkgolide B	1.0	82	0.83
	0.5	42	
	0.1	10	
82	1.0	100	0.09
	0.5	94	
	0.1	60	
96	1.0	100	0.10
	0.5	97	
	0.1	50	
97	1.0	100	0.42
	0.5	68	
	0.1	30	
99	1.0	100	0.31
	0.5	73	
	0.1	42	
103	1.0	97	0.48
	0.5	62	
	0.1	10	
115	1.0	100	0.08
	0.5	100	
	0.1	65	

Pharmacology Example 4 : The aeroallergen-induced bronchial infiltration of eosinophils in the bronchoalveolar lavage fluid.

Adult, male Hartley-strain guinea pigs weighing 492~735 g were sensitized by intraperitoneal injection of 10 ㎍ ovalbumin(OA) mixed in 100-㎎ aluminum hydroxide. And guinea pigs were pretreated with pyrilamine(1.0 ㎎/㎏) intraperitoneally 30 min before aeroallergen challenge. Individual guinea pigs were placed in a two-liter glass chamber and exposed to a five aerosol of OA solution(0.5 ㎎/㎖ in saline containing 0.02 % antifoal emulsion for a period of 10min).

4 hours after aero allergen challenge, the guinea pigs received either vehicle or compounds suspended in 1 % acacia by oral gavage.

24 hours after aero allergen challenge, the animals were euthanized with an i.p. overdose of pentobarbital sodium(100 ㎎/㎏). The abdominal cavity was opened, and the animal was exsaguinated by cutting the abdominal aorta. A midline incision was made through the rib cage, exposing the heart and lungs.

The trachea was cannulated with an 18-gauge stainless steel feeding tube; 20 ㎖/㎏ of prewarmed(37 ℃) physiological saline was instilled and the BALF was gently withdrawn.

BALF(amounting to 60~80 % of the saline infused) was transferred to a 10 ㎖ vacutainer containing 0.10 ㎖ of 15 % EDTA solution and centrifugated at 2400 rpm for 10 min.

The supernatant was poured off, and the cell pellet was suspended in physiological saline equal to the ratio of BALF recovered(㎖) and physiological saline instilled in the lungs(㎖), multiplied by two.

The eosinophils in BALF were counted by Unopette Test 5877.

The mean numbers of eosinophils ± SEM in the BALF of

compound-treated animals and corresponding control "vehicle"-treated animals were compared by student's t-test. A P value of 0.05 or less was considered significont. Table 4 lists results from this assay for inhibition of bronchial eosinophilia for illustrative examples of this invention.

Table 4 : Results for inhibition of bronchial eosinophilia in the guinea pig.

Example	Dose mg/kg, p.o.,+ 4h	Numbers of Guinea pig.	Eosinophils 10^3 cells/*ml* BALF (Mean ± SEM)	% Inhibition
vehicle only	-	10	927 ± 131	-
Ginkgolide B	30	4	1148 ± 305	0
82	30	10	616 ± 145	34
96	30	7	641 ± 134	31

*P< 0.05 as compared to control.

Pharmacology Example 5: PAF induced Lethality in Mice

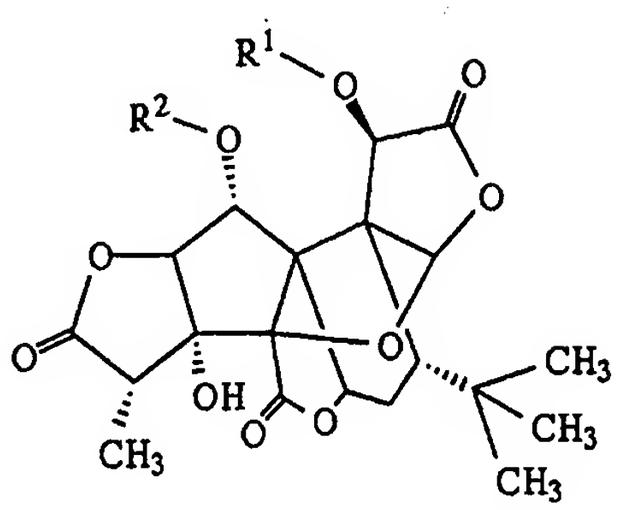
PAF given I.V. (10 μg/kg) to mice causes an immediate hypotensive shock leading to death in 1 hour or less. Compounds were given intraperitoneally (dose of compounds : 10 mg/kg) at 2 minutes before the PAF challenge. Animals alive after 2 hours were counted and the activity of test compounds expressed as % survival corrected for any control(saline treated) animals which survived the PAF challenge. The results are presented in the following table 5.

Table 5: Results for protection of PAF induced Lethality in Mice

Example	Survival rate(%)
control	0
82	100
96	100
115	100

WHAT IS CLAIMED IS;

1. A compound of formula(I) :



(I)

wherein ,

R^2 represents hydrogen or R^1 group; and

R^1 represents -A-Ar, -A-Z-Ar, -C(=O)-Ar, $-SO_2$-Ar, -A-Het. or -A-NR^4R^5,

in which A represents an alkylene group having 1 to 8 carbon atoms, which is unsubstituted or substituted by a straight or branched alkyl chain group having 1 to 5 carbon atoms; Z represents carbon, oxygen, sulfur or nitrogen; Ar represents a phenyl group, a pyridyl group, a naphthyl group, a pyrimidyl group, or a quinolyl group, each of which may be unsubstituted or substituted by one to five substituents selected from the group consisting of hydrogen, halogen, a hydroxy group, a carboxylic acid group, an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 1 to 10 carbon atoms, an alkynyl group having 1 to 10 carbon atoms, a haloalkyl group having 1 to 10 carbon atoms, an alkoxy group having 1 to 10 carbon

atoms, an alkenyloxy group having 1 to 10 carbon atoms, an alkynyloxy group having 1 to 10 carbon atoms, a haloalkoxy group having 1 to 10 carbon atoms, a phenyl group, a phenoxy group, an aralkyl group, an aralkyloxy group, a substituted phenyl group, a substituted phenoxy group, a substituted aralkyl group, or a substituted aralkyloxy group, $-COR^4$, $-CONR^4R^5$, $-CO_2R^4$, $-NHCOR^4$, $-NH(OH)$, $-N(OH)COR^4$, $-CH_2OR^4$, $-OCH_2CO_2R^4$, $-CH_2SR^4$, $-CH_2NR^4R^5$, $-SR^4$, $-OSR^4$, $-SO_2NR^4R^5$, $-NR^4R^5$, $-NR^4SO_2R^5$ in which R^4 and R^5 are the same or different and each is hydrogen, an alkyl group having 1 to 10 carbon atoms or a cycloalkyl group having 3 to 10 carbon atoms, $-SCX_3$ in which X is halogen, $-CN$, $-NO_2$ and -Z-A-Z'- in which Z and A are as defined above and Z' represents carbon, oxygen, sulfur, or nitrogen; Het. represents a cyclic saturated or unsaturated heterocyclic group having one or more nitrogen, oxygen, and/or sulfur atoms.

2. The compound according to claim 1, wherein

R^2 represents hydrogen or R^1 group; and

R^1 represents -A-Ar, -A-Z-Ar, -CO-Ar, $-SO_2$-Ar, -A-Het. or $-A-NR^4R^5$, in which A represents an alkylene group having 1 to 8 carbon atoms selected from methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, heptamethylene and octamethylene group or an alkylene group having 1 to 8 carbon atoms which is substituted by a straight or branched chain alkyl group having 1 to 5 carbon atoms selected from methylmethylene, propylene, methyltrimethylene, dimethylethylene, dimethyltetramethylene,

ethylethylene and dimethyltrimethylene; Z represents carbon, oxygen, sul, which is unsubstituted or substituted by a straight or branched chain alkyl group having 1 to 5 carbon atoms; Z represents carbon, oxygen, sulfur or nitrogen; Het. represents saturated or unsaturated heterocyclic group having one or more nitrogen, oxygen and sulfur atoms selected from morpholinyl, piperidinyl, piperazinyl, triazolyl, imidazolyl, pyrrolidyl, thiazolidinyl and furanyl group; Ar represents a phenyl group, a pyridyl group, a naphthyl group, a pyrimidyl group, or a quinolyl group, each of which may be unsubstituted or substituted by one to five substituents selected from hydrogen; halogen selected from fluoro, chloro, bromo and iodo; a hydroxy group; a carboxylic acid group; an alkyl group having 1 to 10 carbon atoms selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, 1-methylbutyl, n-hexyl, 1-methylpentyl, n-heptyl, 4-methylhexyl, 1-ethylpentyl, 1, 4-dimetylpentyl, n-octyl, 6-methylheptyl and 2-ethylhexyl; an alkenyl group having 1 to 10 carbon atoms selected from vinyl, allyl, 3-pentenyl and 1-hexenyl; alkynyl group having 1 to 10 carbon atoms; a haloalkyl group having 1 to 10 carbon atoms selected from fluoromethyl, chloromethyl, bromomethyl, iodomethyl, trifluoromethyl, trifluoroethyl, trifluoropropyl, trifluoromethylethyl and trifluoromethylpropyl group; an alkoxy group having 1 to 10 carbon atoms selected from methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, isobutoxy, *tert*-butoxy, *n*-pentyloxy, isopentyloxy, *n*-hexyloxy, *n*-heptyloxy, 1-propylbutoxy, *n*-octyloxy, 5-methylhexyloxy, 2-ethylhexyloxy and 1,6-dimethylhexyloxy; an alkenyloxy group having 1 to 10 carbon atoms; an alkynyloxy group having 1 to 10

carbon atoms; a haloalkoxy group having 1 to 10 carbon atoms; a phenyl group; a phenoxy group; an aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl and 4-phenylbutyl; an aralkyloxy group selected from benzyloxy, 2-phenylethoxy, 3-phenylpropoxy and 4-phenylbutoxy group; a substituted phenyl group selected from 2-chlorophenyl, 2-bromophenyl, 2-fluorophenyl, 2-iodophenyl, 3-fluorophenyl, 2,3-dichlorophenyl, 4-hydroxyphenyl, 2-methylphenyl, 4-methylphenyl, 3-ethylphenyl, 4-propylphenyl, 4-isopropylphenyl, 4-butylphenyl, 4-*tert*-butylphenyl, 4-pentylphenyl, 2,4-dimethylphenyl group, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 3-ethoxyphenyl, 2-propoxyphenyl, 4-butoxyphenyl and 2,4-dimethoxyphenyl ; a substituted phenoxy group selected from 3,4,5-trimethoxyphenoxy, 2-chlorophenoxy, 2,3-dichlorophenoxy, 4-hydroxyphenoxy, 2-methoxyphenoxy, 4-butylphenoxy and 2,4-dimethylphenoxy; a substituted aralkyl group selected from chlorobenzyl, bromobenzyl, fluorobenzyl, iodobenzyl, dichlorobenzyl, dibromobenzyl, difluorobenzyl, hydroxybenzyl, methylbenzyl, halomethylbenzyl, methoxybenzyl and trimethoxybenzyl; a substituted aralkyloxy group selected from chlorobenzyloxy, dimethylbenzyloxy, trifluoromethylbenzyloxy and trimethoxybenzyloxy; $-COR^4$; $-CONR^4R^5$; $-CO_2R^4$; $NHCOR^4$; $N(OH)H$; $N(OH)COR^4$; $-CH_2OR^4$; $-OCH_2CO_2R^4$; $-CH_2SR^4$; $-CH_2NR^4R^5$; $-SR^4$; $-OSR^4$; $-SO_2NR^4R^5$; $-NR^4R^5$; $-NR^4SO_2R^4$, in which R^4 and R^5 are the same or different and each is hydrogen, an alkyl group having 1 to 10 carbon atoms or a cycloalkyl group having 3 to 10 carbon atoms; $-SCX_3$, in which X represents halogen; $-CN$; $-NO_2$; or cyclic

linked substituent, -Z-A-Z'-, in which Z and A are as defined above and Z' represents carbon, oxygen, sulfur, or nitrogen, selected from $-OCH_2O-$, $-OCH_2CH_2O-$, $-OCH_2CH_2CH_2O-$, $-OCH_2CH_2N-$, $-NCH_2CH_2N-$, $-OCH_2CH_2-$, $-NCH_2CH_2-$, $-NCH_2CH_2CH_2-$, $-SCH_2S-$, $-SCH_2CH_2S-$, $-SCH_2-$, $-SCH_2CH_2-$ or $-SCH_2CH_2CH_2-$.

3. The compound according to claim 1, wherein

R^2 is hydrogen, and

R^1 is $-CH_2-Ar$, $-CH_2CH_2-Ar$, $-CH_2CH_2CH_2-Ar$, $-CH_2O-Ar$,

$-CH_2CH_2O-Ar$, $-CH_2CH_2CH_2O-Ar$, $-\overset{O}{\overset{\|}{C}}-Ar$ or $-SO_2-Ar$,

in which Ar is a phenyl group, a pyridyl group, a pyrimidyl group or quinolyl group, each of which is unsubstituted or substituted by one to five substituents selected from the group consisting of hydrogen, halogen, a hydroxy group, an alkyl group having 1 to 10 carbon atoms, a haloalkyl group having 1 to 10 carbon atoms, an alkoxy group having 1 to 10 carbon atoms, a haloalkoxy group having 1 to 10 carbon atoms, a phenyl group, a phenoxy group, an aralkyl group, an aralkyloxy group,

$-\overset{O}{\overset{\|}{C}}R^4$, $-\overset{O}{\overset{\|}{C}}NR^4R^5$, $-CO_2R^4$, $-CH_2OR^4$, $-NR^4R^5$, $-CH_2NR^4R^5$, $-CN$, $-NO_2$

and -Z-A-Z'-.

4. A compound according to claim 1, wherein said compound is selected from the group consisting of

10-benzyloxy-Ginkgolide B,

10-(2',4'-dichlorobenzyloxy)-Ginkgolide B,

10-(4'-chlorobenzyloxy)-Ginkgolide B,

10-(4'-methoxybenzyloxy)-Ginkgolide B,

10-(3',4',5',-trimethoxybenzyloxy)-Ginkgolide B,

10-(2'-methylbenzyloxy)-Ginkgolide B,

1,10-bis(2'-methylbenzyloxy)-Ginkgolide B,

10-(4'-methylbenzyloxy)-Ginkgolide B,

10-(3'-phenoxypropoxy)-Ginkgolide B,

10-(2'-phenylethoxy)-Ginkgolide B,

10-(3',4',5',-trimethoxybenzoyloxy)-Ginkgolide B,

10-(4'-phenylbenzyloxy)-Ginkgolide B,

10-piperonyloxy-Ginkgolide B,

10-(2',3',4',5',6'-pentafluorobenzyloxy)-Ginkgolide B,

10-(2',4'-difluorobenzyloxy)-Ginkgolide B,

10-(4'-fluorobenzyloxy)-Ginkgolide B,

10-(2'-fluorobenzyloxy)-Ginkgolide B,

10-benzoyloxy-Ginkgolide B,

1-benzoyloxy-Ginkgolide B,

1,10-bis(2',4'-dichlorobenzyloxy)-Ginkgolide B,

10-(3'-trifluoromethylbenzyloxy)-Ginkgolide B,

10-benzenesulfonyloxy-Ginkgolide B,

10-(3'-methoxybenzyloxy)-Ginkgolide B,

10-(4'-trifluoromethylbenzyloxy)-Ginkgolide B,

1,10-bis(4'-trifluoromethylbenzyloxy)-Ginkgolide B,

10-(4'-hydroxybenzyloxy)-Ginkgolide B,

10-(4'-ethoxybenzyloxy)-Ginkgolide B,

10-(3'-bromobenzyloxy)-Ginkgolide B,

10-(4'-iodobenzyloxy)-Ginkgolide B,

10-(2',3',4'-trihydroxybenzyloxy)-Ginkgolide B,

10-(2'-iodobenzyloxy)-Ginkgolide B,

10-(2'-hydroxybenzyloxy)-Ginkgolide B,

10-(3'-iodobenzyloxy)-Ginkgolide B,

10-(3'-hydroxybenzyloxy)-Ginkgolide B,

10-(2'-bromobenzyloxy)-Ginkgolide B,

10-(3',4'-dihydroxybenzyloxy)-Ginkgolide B,

10-(4'-bromobenzyloxy)-Ginkgolide B,

10-(2'-chlorobenzyloxy)-Ginkgolide B,

10-(3'-chlorobenzyloxy)-Ginkgolide B,

10-(2',4',-dibromobenzyloxy)-Ginkgolide B,

10-(2',3',4',5',6'-pentachlorobenzyloxy)-Ginkgolide B,

10-(2',3',4',5',6'-pentabromobenzyloxy)-Ginkgolide B,

10-(2',3',4',5',6'-pentaiodobenzyloxy)-Ginkgolide B,

10-(2'-methoxybenzyloxy)-Ginkgolide B,

10-(3'-methoxybenzyloxy)-Ginkgolide B,

10-(2'-ethoxybenzyloxy)-Ginkgolide B,

10-(3'-ethoxybenzyloxy)-Ginkgolide B,

10-(2'-propoxybenzyloxy)-Ginkgolide B,

10-(3'-propoxybenzyloxy)-Ginkgolide B,

10-(4'-propoxybenzyloxy)-Ginkgolide B,

10-(2'-isopropoxybenzyloxy)-Ginkgolide B,

10-(3'-isopropoxybenzyloxy)-Ginkgolide B,

10-(4'-isopropoxybenzyloxy)-Ginkgolide B,

10-(4'-methlbenzyloxy)-Ginkgolide B,

10-(2'-ethylbenzyloxy)-Ginkgolide B,

10-(3'-ethylbenzyloxy)-Ginkgolide B,

10-(4'-ethylbenzyloxy)-Ginkgolide B,

10-(2'-propylbenzyloxy)-Ginkgolide B,

10-(3'-propylbenzyloxy)-Ginkgolide B,

10-(2'-bromoethoxy)-Ginkgolide B,

10-(2'-iodoethoxy)-Ginkgolide B,

10-(2'-(1"-piperidinyl)-ethoxy)-Ginkgolide B,

10-(2'-(1"-morphorinyl)-ethoxy)-Ginkgolide B,

10-(2'-(1"-(1",2",4"-triazolyl)-ethoxy))-Ginkgolide B,

10-(2'-(1"-piperazinyl))-Ginkgolide B,

10-(2'-(1"-pyrrolidinyl)-ethoxy)-Ginkgolide B,

10-(3,5-dimethyl-2-pyridinyl)-methoxy-Ginkgolide B,

10-(4-methoxy-3,5-dimethyl-2-pyridinyl)-methoxy-Ginkgolide B,

10-(3,5-dimethyl-4-nitro-2-pyridinyl)-methoxy-Ginkgolide B,

10-(2-pyridinyl)-methoxy-Ginkgolide B,

10-(5-butyl-2-pyridinyl)-methoxy-Ginkgolide B,

10-(2-pyridinyl)-ethoxy-Ginkgolide B,

10-(2-quinolinyl)-methoxy-Ginkgolide B,

10-(3,5-dimethyl-4-amino-2-pyridinyl)-methoxy-Ginkgolide B,

10-(3,5-dimethyl-4-nitro-2-pyridnyl)-methoxy-

Ginkgolide B,

10-(3,5-dimethyl-4-hydroxy-2-pyridinyl)-methoxy-

Ginkgolide B,

10-(3,5-dimethyl-4-hydroxyamino-2-pyridinyl)-methoxy-

Ginkgolide B,

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Ginkgolide B,

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10-(6-chloro-3-pyridinyl)-methoxy-Ginkgolide B,

10-(3-pyridinyl)-methoxy-Ginkgolide B,

10-(4-pyridinyl)-methoxy-Ginkgolide B,

10-(2-(4-ethoxypyridinyl))-methoxy-Ginkgolide B,

10-(2-(4-nitropyridinyl))-methoxy-Ginkgolide B,

10-(2-(6-methyl-3-propoxypyridinyl))-methoxy-

Ginkgolide B,

10-(2-(4-hydroxyaminopyridinyl))-methoxy-Ginkgolide B,

10-(2-(5-methoxyethoxymethoxypyridinyl))-methoxy-

Ginkgolide B,

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10-(2',5'-dihydroxybenzyloxy)-Ginkgolide B,

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10-(3',4',5'-trihydroxybenzyloxy)-Ginkgolide B,

10-(2'-vinylbenzyloxy)-Ginkgolide B,

10-(3'-vinylbenzyloxy)-Ginkgolide B,

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10-(2'-allylbenzyloxy)-Ginkgolide B,

10-(2'-trifluoromethylbenzyloxy)-Ginkgolide B,

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10-(2'-fluoromethylbenzyloxy)-Ginkgolide B,

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10-(4'-allylbenzyloxy)-Ginkgolide B,

10-(3'-fluoromethylbenzyloxy)-Ginkgolide B,

10-(4'-fluoromethylbenzyloxy)-Ginkgolide B,

10-(2'-chloromethylbenzyloxy)-Ginkgolide B,

10-(3'-chloromethylbenzyloxy)-Ginkgolide B,

10-(4'-chloromethylbenzyloxy)-Ginkgolide B,

10-(2'-bromomethylbenzyloxy)-Ginkgolide B,

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10-(3'-fluoromethoxybenzyloxy)-Ginkgolide B,

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10-(4'-bromomethoxybenzyloxy)-Ginkgolide B,

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10-(3'-trifluoromethoxybenzyloxy)-Ginkgolide B,

10-(4'-trifluoromethoxybenzyloxy)-Ginkgolide B,

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10-(3'-trichloromethoxybenzyloxy)-Ginkgolide B,

10-(4'-trichloromethoxybenzyloxy)-Ginkgolide B,

10-(2'-tribromomethoxybenzyloxy)-Ginkgolide B,

10-(3'-tribromomethoxybenzyloxy)-Ginkgolide B,

10-(4'-tribromomethoxybenzyloxy)-Ginkgolide B,

10-(2'-phenoxybenzyloxy)-Ginkgolide B,

10-(2'-benzylbenzyloxy)-Ginkgolide B,

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10-(4'-phenbutoxy)-Ginkgolide B,

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10-(4'-(3"-phenpropyl)-benzyloxy)-Ginkgolide B,

10-(4'-(4"-phenbutyl)-benzyloxy)-Ginkgolide B,

10-(4'-(2"-chlorophenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(2"-bromophenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(2"-fluorophenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(2"-bromophenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(2"-iodophenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(3"-fluorophenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(2",3"-dichlorophenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(4"-hydroxyphenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(2"-methylphenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(4"-methylphenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(3"-ethylphenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(4"-propylphenyl)-benzyloxy)-Ginkgolide B,

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10-(4'-(4"-butylphenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(4"-pentylphenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(2",4"-dimethylphenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(2"-trifluoromethylphenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(2"-methoxyphenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(3"-methoxyphenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(4"-methoxyphenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(3"-ethoxyphenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(2"-propoxyphenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(4"-butoxyphenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(2",4"-dimethoxyphenyl)-benzyloxy)-Ginkgolide B,

10-(4'-(3",4",5"-trimethoxyphenoxy)-benzyloxy)-Ginkgolide B,

10-(4'-(2"-chlorophenoxy)-benzyloxy)-Ginkgolide B,

10-(4'-(2",3"-dichlorophenoxy)-benzyloxy)-Ginkgolide B,

10-(4'-(4"-hydroxyphenoxy)-benzyloxy)-Ginkgolide B,

10-(4'-(2"-methoxyphenoxy)-benzyloxy)-Ginkgolide B,

10-(4'-(4"-butylphenoxy)-benzyloxy)-Ginkgolide B,

10-(4'-(2",4"-dimethylphenoxy)-benzyloxy)-Ginkgolide B,

10-(4'-(4"-chlorobenzyl)-benzyloxy)-Ginkgolide B,

10-(4'-(4"-bromobenzyl)-benzyloxy)-Ginkgolide B,

10-(4'-(4"-fluorobenzyl)-benzyloxy)-Ginkgolide B,

10-(2'-nitrobenzyloxy)-Ginkgolide B,

10-(3'-nitrobenzyloxy)-Ginkgolide B,

10-(4'-nitrobenzyloxy)-Ginkgolide B,

10-(2'-cyanobenzyloxy)-Ginkgolide B,

10-(3'-cyanobenzyloxy)-Ginkgolide B,

10-(4'-cyanobenzyloxy)-Ginkgolide B,

10-(2'-aminobenzyloxy)-Ginkgolide B,

10-(3'-aminobenzyloxy)-Ginkgolide B,

10-(4'-aminobenzyloxy)-Ginkgolide B,

10-(2'-dimethylaminobenzyloxy)-Ginkgolide B,

10-(3'-dimethylaminobenzyloxy)-Ginkgolide B,

10-(4'-dimethylaminobenzyloxy)-Ginkgolide B,

10-(3',4'-dihydroxybenzyloxy)-Ginkgolide B,

10-(3,5-dimethyl-4-hydroxybenzyloxy)-Ginkgolide B,

10-(3,5-di-*tert*-butyl-4-hydroxybenzyloxy)-Ginkgolide B,

10-(4-hydroxy-3-methoxybenzyloxy)-Ginkgolide B,

10-(3,5-dimethoxy-4-hydroxybenzyloxy)-Ginkgolide B and

10-(3-amino-4-hydroxy-5-methyl-benzyloxy)-Ginkgolide B.

5. A pharmaceutical composition comprising a compound of formula(I) as claimed in claim 1 and a pharmaceutically acceptable carrier.

6. A pharmaceutical composition for the prevention or treatment of PAF-induced diseases or allergen-induced diseases comprising a compound of formula(I) as claimed in claim 1.

7. A method for treating asthma in a mammal which comprises administering to the mammal an antiasthmatic amount of a compound as claimed in claim 1

8. A method for treating anaphylatic and septic shock in a mammal which comprises administering to said mammal an effective amount of a compound as claimed in claim 1.

9. A method for treating psoriasis in a mammal which comprises administering to the mammal an effective amount of a compound as claimed in claim 1.

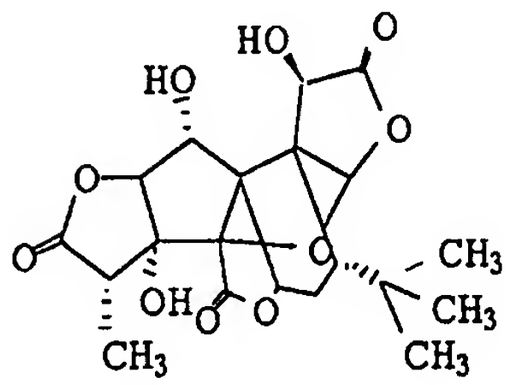
10. A method for treating bowel necrosis in a mammal which comprises administering to the mammal an effective amount of a compound as claimed in claim 1.

11. A method for treating adult respiratory distress syndrome in a mammal which comprises administering to the mammal an effective amount of a compound as claimed in claim 1.

12. A method for treating transplant rejection in a mammal which comprises administering to the mammal an effective amount of a compound as claimed in claim 1.

13. A process for preparing a compound of formula(I) as claimed in claim

1, which comprises reacting a compound of formula(II) and a compound of formula R^1-L in the presence of base and an organic solvent.



(II)

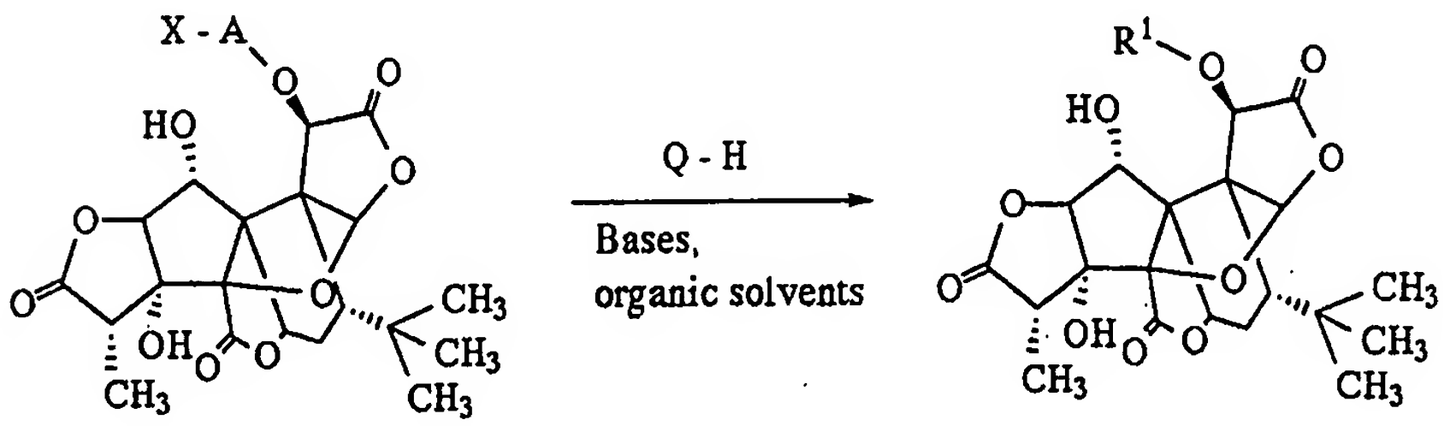
wherein L represents halogen, 4-methylbenzenesulfonyloxy, methanesulfonyloxy, 4-nitrobenzenesulfonyloxy, 4 bromobenzene-sulfonyloxy or trifluoromethanesulfonyloxy group.

14. The process according to claim 13, wherein said base is selected from the group consisting of Ag_2O, triethylamine, an alkali carbonate, an alkali bicarbonate, an alkali hydroxide, MH, MNH_2, MOR^4, MR^4, R^4R^5 NM, $MN(TMS)_2$ and a mixtures bases thereof, wherein M is alkali metal selected from the group consisting of Li, Na and K, TMS is trimethylsilyl group, and R^4 and R^5 are as defined in claim 1.

15. The process according to claim 13, wherein said organic solvent is selected from the group consisting of tetrahydrofuran, acetone, ethylacetate, dimethylformamide, dimethylsulfoxide, pyridine, dioxane, methanol, ethanol, 2-methoxyethanol and a mixtures thereof.

16. The process according to claim 13, wherein said reaction is carried out at 0~70 ℃.

17. A process for preparing a compound of formula(I') as below, which comprises reacting a compound of formula(III) as below with Q-H in the presence of a base and an organic solvent:

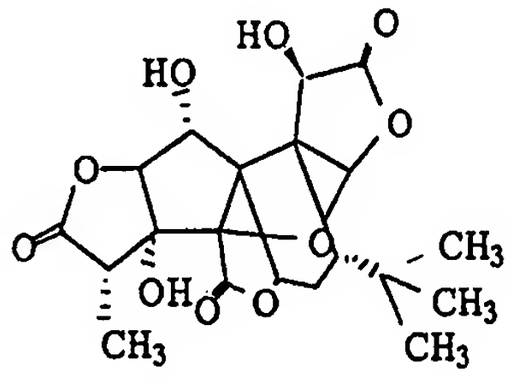


(III) (I')

wherein, A represents an alkylene group having 1 to 8 carbon atoms, which is unsubstituted or substituted by a straight or branched alkyl chain group having 1 to 5 carbon atoms; the base is selected from the group consisting of Ag_2O, triethylamine, an alkali carbonate, an alkali bicarbonate, an alkali hydroxide, MH, MNH_2, MOR^4, MR^4, R^4R^5NM, $MN(TMS)_2$ and mixtures bases thereof, wherein M is alkali metal selected from the group consisting of Li, Na and K, and TMS is a trimethylsilyl group; the organic solvent is selected from the group consisting of tetrahydrofuran, acetone, ethylacetate, dimethylformamide, dimethylsulfoxide, pyridine, dioxane, methanol, ethanol, 2-methoxyethanol and mixtures thereof; Q represents Het. or NR^4R^5, in which R^4 and R^5 are the same or different and each is hydrogen, an alkyl group having 1 to carbon atoms or a cycloalkyl

group having 3 to 10 carbon atoms and Het. represents a cyclic saturated or unsaturated heterocyclic group having one or more nitrogen, oxygen, and/or sulfur atoms; and X represents halogen selected from the group consisting of fluoro, chloro, bromo and iodo.

18. A process according to claim 17, further comprising preparing a compound of formula(III) by reacting a compound of formula(II) with a compound of formula X-A-OY in the presence of a base and an organic solvent, wherein Y represents 4-methylbenzenesulfonyl, methanesulfonyl, 4-nitrobenzenesulfonyl, 4-bromobenzene sulfonyl or trifluoromethanesulfonyl.



(II)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 94/00187

A. CLASSIFICATION OF SUBJECT MATTER

IPC[6]: C 07 D 493/22 //(C 07 D 493:22, 307:00); A 61 K 35/78
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[6]: C 07 D 493/22 // (C 07 D 493:22, 307:00); A 61 K 35/78

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AT

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS, WPIL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 93/06 107 A1 (SUNKYONG INDUSTRIES CO.) 01 April 1993 (01.04.93), claims 1-13.	1,5,6,13,17
A	DE 4 212 019 A1 (SOCIETE DE CONSEILS DE RECHERCHES) 15 October 1992 (15.10.92), claims 1-9.	1,5,6,13,17

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 March 1995 (28.03.95)	19 April 1995 (19.04.95)
Name and mailing address of the ISA/ AT AUSTRIAN PATENT OFFICE Kohlmarkt 8-10 A-1014 Vienna Facsimile No. 1/53424/535	Authorized officer Brus e.h. Telephone No. 1/5337058/32

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 94/00187

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 7-12
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 7-12 are considered to be a method for treatment of the human or animal body by therapy and are subject matters which the International Searching Authority is not requested to search (rule 39.1(iv)PCT), all claims have been searched completely. Relevant documents are cited with in the search report.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATI NAL SEARCH REPORT
Information on patent family members

International application No.
PCT/KR 94/00187

In Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
WO A1 9306107	01-04-93	EP A1 642515	15-03-95
		JP T2 6505999	07-07-94
DE A1 4212019	15-10-92	AU A1 14704/92	15-10-92
		AU B2 647350	17-03-94
		BE AD 1005089	13-04-93
		CA AA 2065501	10-10-92
		CH A 684193	29-07-94
		DK AO 474/92	08-04-92
		DK A 474/92	10-10-92
		ES AA 2038560	16-07-93
		ES BA 2038560	16-02-94
		FI AO 921523	07-04-92
		FI A 921523	10-10-92
		FR A1 2675145	16-10-92
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		GB AO 9107425	22-05-91
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		GR B 1001019	31-03-93
		IT AO 92500807	03-04-92
		JP A2 5255341	05-10-93
		LU A 88094	15-10-92
		NL A 9200549	02-11-92
		NO AO 921388	08-04-92
		NO A 921388	12-10-92
		NZ A 242188	25-06-93
		PT A 100363	31-03-94
		SE AO 9201125	08-04-92
		SE A 9201125	10-10-92
		US A 5241084	31-08-93
		ZA A 9202352	30-12-92